

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

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Breast cancer susceptibility variants frequently show heterogeneity in associations by tumor subtype¹⁻³. 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 (FDR) <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. The odds ratios of polygenic risk scores (PRSs), which included 330 variants, for the highest 1% quantiles compared to middle quantiles were 5.63 and 3.02 for luminal A-like and triple-negative disease, respectively. These findings provide an improved understanding of genetic predisposition to breast cancer subtypes and will inform the development of subtype-specific polygenic risk scores.

Based on the largest GWAS to date from the Breast Cancer Association Consortium (BCAC), over 170 independent breast cancer susceptibility variants have been identified. Many of these variants show differential associations by tumor subtypes, particularly ER-positive versus ER-negative or triple-negative disease¹⁻³. However, prior GWAS have not simultaneously accounted for the high correlations between multiple, correlated tumor markers, such as ER, PR, HER2 and grade, to identify specific 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 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 **Extended Data Figure 1**. To identify variants 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 the results were combined with those from the 11 other GWAS using fixed-effects meta-analysis.

To identify breast cancer susceptibility variants 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 variants and intrinsic-like subtypes defined by combinations of ER, PR, HER2 and grade⁸ (**Online Methods**): (1) luminal A-like, (2) luminal B/HER2-negative-like, (3) luminal B-like, (4) HER2-enriched-like and (5) triple-negative 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**).

Among *BRCA1* mutation carriers who are prone to develop triple-negative disease⁹, we estimated per-allele hazard ratios (HRs) within a retrospective cohort analysis framework. We assumed estimated ORs for BCAC triple-negative cases and estimated HRs from CIMBA *BRCA1* carriers approximated the same underlying relative risk⁹, and we used a fixed-effect meta-analysis to combine these results (**Online**

Methods). Among all novel variants, we used the two-stage polytomous model to test for heterogeneity in associations across subtypes, globally and by tumor-specific markers (**Online Methods**).

Overall, we identified 32 novel independent susceptibility loci marked by variants with $P < 5.0 \times 10^{-8}$ (**Figure 1, Supplementary Table 5-7, Supplementary Figure 1-5**): 22 variants using standard logistic regression, 16 variants using the two-stage polytomous model (eight of which were detected by standard logistic regression) and three variants in the CIMBA/BCAC-triple-negative meta-analysis (rs78378222 was also detected by the two-stage polytomous model in BCAC). Fourteen additional variants ($P < 5.0 \times 10^{-8}$) were excluded, 13 because they lacked evidence of association independent of known susceptibility variants 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 in the leave-one-out country analysis following exclusion of studies from the USA (**Supplementary Figure 6**). **Supplementary Figures 7-8** and **Supplementary Table 11** show associations between all 32 variants and the intrinsic-like subtypes.

Fifteen of the 32 variants showed heterogeneity evidence (FDR < 0.05) according to the global heterogeneity test (**Figure 2, Supplementary Table 12**). ER (7 variants) and grade (7 variants) most often contributed to observed heterogeneity (marker-specific $P < 0.05$), followed by HER2 (4 variants) and PR (2 variants). rs17215231, identified in the CIMBA/BCAC-triple-negative meta-analysis, was the only variant found exclusively associated with triple-negative disease (OR=0.85, 95%CI=0.81-0.89). rs2464195, also identified in the CIMBA/BCAC-triple-negative meta-analysis, was associated with both triple-negative (OR=0.93, 95%CI=0.91-0.96) and

luminal B-like subtypes (OR=0.96, 95%CI=0.92-0.99; **Supplementary Table 11**) and is in linkage disequilibrium (LD; $r^2=0.62$) with rs7953249, which is differentially associated with risk of ovarian cancer subtypes¹⁰. Five variants showed associations with luminal and non-luminal subtypes in opposite directions (**Figure 3**). Four variants were associated in opposite directions with luminal A-like and triple-negative 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 tumor-marker heterogeneity test showed associations for rs78378222 with ER ($P_{ER} = 7.0 \times 10^{-6}$) and HER2 ($P_{HER2} = 2.07 \times 10^{-4}$), rs206435 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 ($P_{ER} = 4.3 \times 10^{-3}$) with ER. rs7924772 showed opposite case-control associations between HER2-negative and HER2-positive subtypes and, consistent with these findings, was exclusively associated with HER2 ($P_{HER2} = 1.4 \times 10^{-6}$; **Figure 3**). 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, $P = 1.5 \times 10^{-4}$; -). Prior analyses¹¹ did not find rs78378222 associated with breast cancer risk, likely due to its opposite effects between subtypes.

Candidate causal variants were defined (CCVs; **Online Methods**) for each novel locus and we investigated the CCVs in relation to previously-annotated enhancers in primary breast cells¹². 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 identified with associations in opposite directions between subtypes, at least one CCV per locus overlapped an “ANYSWITCH” enhancer (**Figure 4**). For example, rs78378222 overlapped an ACTIVE enhancer in basal cells, PRIMED in luminal progenitor cells and OFF in mature luminal cells. In comparison, 63% of the loci with consistent direction of associations across subtypes overlapped with an “ANYSWITCH” enhancer (**Supplementary Table 13-14**). These results suggest that some variants may modulate enhancer activity in a cell-type specific manner, thus, differentially influencing risk of tumor subtypes.

We used INQUIST to intersect CCVs with functional annotation data from public databases to identify potential target genes¹ (**Supplementary Note, Supplementary Table 15**). We predicted 179 unique target genes for 26 of the 32 independent signals. Notably, rs78378222 has been reported associated with *TP53* mRNA levels in blood and adipose tissue¹¹, which we did not replicate in breast tissue. However, our findings of rs78378222 overlapping a cell type-specific regulatory element in breast basal epithelial cells, implicates enhancer function as another potential *TP53* transcriptional control mechanism. 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. Four target genes were previously predicted by INQUISIT^{13,14}, *POLR3C*, *RNF115*, *SOX4* and *TBX3*— a known somatic breast cancer

driver gene¹⁵ – and genes implicated by transcriptome-wide association studies (*LINC00886*¹⁶ and *YBEY*¹⁷).

We used LD-regression to investigate genetic correlations^{18,19} between subtypes and compare enrichment of genomic features²⁰ between luminal A-like and triple-negative subtypes (**Online Methods**). All subtypes were moderately- to highly correlated, with luminal A-like and triple-negative having a correlation of 0.46 (SE=0.05). The correlation in breast cancer of *BRCA1* carriers and triple-negative was 0.83 (SE=0.08), suggesting a high-degree of similarity in the genetic basis between these subtypes (**Figure 5; Supplementary Table 16**). To compare genomic enrichment, we first evaluated 53 annotations and found triple-negative 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, $P = 4.0 \times 10^{-4}$); however, no annotations significantly differed between luminal A-like and triple-negative tumors (**Supplementary Table 17, Supplementary Figure 9**). Investigating cell-specific enrichment of histone markers H3K4me1, H3K3me3, H3K9ac and H3K27ac (**Supplementary Note**) found both luminal-A and triple-negative subtypes enriched for gastrointestinal cell types and suppression of central nervous system cell types (**Supplementary Figure 10**).

The proportion of genome-wide chip heritability explained by the 32 novel variants, plus 178 previously identified variants^{1,2,21}, was 54.2%, 37.6% and 26.9% for luminal A-like, triple-negative and *BRCA1* carriers, respectively (**Table 1, Supplementary Table 18**). These 210 variants explained approximately 18.3% of the two-fold familial relative risk for invasive breast cancer, while all reliably imputable

variants on the OncoArray explained 37.1% (**Online Methods**). The per-standard deviation ORs between PRSs for luminal-A like and triple-negative subtypes (**Online Methods**), that included 313 published variants²² and 17 novel variants that were independent of the 313 variants (**Supplementary Table 19**), was 1.83 (95% CI=1.78-1.88) and 1.65 (1.57-1.73), with corresponding area under receiver-operator curves of 66.09 and 63.58, respectively (**Extended Data Figure 2-6**).

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 subtypes to inform development of subtype-specific PRSs²². However, to expand the generalizability of our findings, these analyses should be replicated and expanded in multi-ancestry populations.

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Figure Legends for main text

Figure 1. Ideogram of all the independent genome-wide significant breast cancer susceptibility variants in overall, subtypes, BCAC triple-negative (TN) and CIMBA *BRCA1* carriers meta-analysis. The 32 novel variants are labeled with arrows. The other significant variants are within ± 500 or LD > 0.3 with previously reported variants.

Figure 2. Heatmap and clustering of p-values from marker specific heterogeneity test for 32 breast cancer susceptibility loci ($n = 106,278$ invasive cases, $n = 91,477$ controls). P-values are for associations between the most significant variants 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. P-values are raw p-values from two-tailed z-test statistics. Fifteen variants in red color were significant according to the global heterogeneity tests (FDR < 0.05), of which 14 were identified by methods accounting for tumor heterogeneity. TN, triple negative.

Figure 3. Susceptibility variants 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 variants and risk for breast cancer intrinsic-like subtypes² estimated from the first-stage of the two-stage polytomous regression fixed-effects model ($n = 106,278$ invasive cases, $n = 91,477$ controls). 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 variants 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. MAF, minor allele frequency.

Figure 4. Heatmap of candidate causal variants (CCVs) overlapping with enhancer states in primary breast subpopulations for five variants 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 16** 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 variants and all reliably genome-wide imputable variants¹

Phenotype	Genetic variance for 210 identified susceptibility variants ²	Genetic variance for 32 newly identified variants 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 BRCA1 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 variants included 178 variants previously identified or replicated^{1,2} and 32 newly identified variants 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 variant, β_m is the true log odds ratio for the m th variant and M are the total number of causal variants among the GWAS variants. (**Online Methods**).

⁴ Proportion of genetic variance explained by 210 identified GWAS significant variants 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**).

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 ~96% of *in-situ* cases were missing some or all of the tumor markers and *in-situ* cases potentially have different tumor correlations compared to invasive cases, which could potentially bias the estimates from Expectation-Maximization algorithm (**Supplementary 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 **Supplementary 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 Expectation-Maximization 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 variants (including bi-allelic and multi-allelic single nucleotide polymorphisms (SNPs) and small indels) 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 variants, from each component GWAS with an imputation quality score of >0.3. We restricted analysis to variants 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 variants 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 these¹⁻³. We defined known breast cancer susceptibility variants as those variants that were identified or replicated in prior BCAC analyses^{1,2}. To help ensure that novel, independent susceptibility variants were identified, we excluded from these analyses variants within 500 kb of a previously published variant. These excluded regions have

been subject to a separate, fine-mapping conditional analyses that are focused on identifying additional independent susceptibility variants in these regions¹⁴.

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 variants. 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 variants with imputation quality scores (r^2) ≥ 0.3 and minor allele frequency (MAF) >0.005 . We excluded variants located within ± 500 kb of, or in LD ($r^2 \geq 0.1$) with known susceptibility variants²¹. 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 Sullivan²³.

Subtypes analysis of BCAC data

We described the two-stage polytomous logistic regression in more detail elsewhere^{4,24} (**Supplementary Note**). In brief, this method allows for efficient testing of a variant-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 variants 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. In the two-stage model, the frequency of different tumor subtypes corresponding to different combinations of the tumor characteristics are allowed to vary freely through the model-free specification of the intercepts of the first-stage polytomous model (α_m ,

see **Supplementary Note** for details), in other words, the intercepts are kept saturated. As these parameters are estimated from the data itself, the methodology accounts for the correlation among the tumor markers in a robust manner that does not require strong modelling assumptions.

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)⁴. 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 variants with MAF >0.01 (~10.0 million) and $r^2 \geq 0.3$, and excluded variants within ± 500 kb of, or in LD ($r^2 \geq 0.1$) with known susceptibility variants. A MAF >0.01 was chosen to ensure an adequate sample size to generate stable estimates. We reported variants that passed the p-value threshold of $P < 5.0 \times 10^{-8}$ in either the fixed- or mixed-effect models.

Both fixed/mixed-effect models adjusted for top ten PCs and age. As age is correlated with the tumor characteristics²⁵, we added age as a covariate to improve the statistical power of Expectation-Maximization (EM) algorithm. Country was not adjusted

for in the subtype analyses, since doing so required adequate sample size of each subtype in each country to allow for convergence of the two-stage polytomous model. Instead, 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 variants and breast cancer risk for *BRCA1* mutation carriers using a score test statistic based on the retrospective likelihood of observing the variant genotypes conditional on breast cancer phenotypes (breast cancer status and censoring time)²⁶. 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 correlations²⁷. 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

As the great majority of *BRCA1* related breast cancers are triple-negative²⁸, we performed a meta-analysis with the BCAC triple-negative results to increase the power to detect associations for the triple-negative subtype. We performed a fixed-effects

meta-analysis of the results from BCAC triple-negative cases and CIMBA *BRCA1* mutation carriers, using an inverse-variance fixed-effects approach implemented in METAL²⁹. 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 triple-negative 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 variant and analyzed association for all remaining variants within ± 500 kb of the lead variants, irrespective of LD. Second, we confirmed the independence of 20 variants that were located within ± 2 MB of a known susceptibility region by conditioning the identified signals on the nearby known signal. Since these 20 variants 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 error³⁰.

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 variants 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 procedure³¹. Among the variants 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 grade⁸: (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) triple-negative (ER-, PR-, HER2-). Further, we conducted sensitivity analysis by fitting a standard polytomous model among cases with complete data on the five-intrinsic-like subtypes for the 32 novel variants and compared these results with the results from two-stage polytomous model accounting for missing tumor data.

Candidate causal variants

We defined credible sets of candidate causal variants (CCVs) as variants located within ± 500 kb of the lead variants in each novel region and with P values within 100-fold of magnitude of the lead variants. This is approximately equivalent to selecting variants whose posterior probability of causality is within two orders of magnitude of the most significant variant^{32,33}. This approach was applied for detecting a set of potentially causal variants for all 32 identified variants. For the novel variants located within ± 2 Mb of the known signals, we used the conditional P values to adjust for the known signals' associations.

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.¹². 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 described¹². 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 regression¹⁸⁻²⁰ 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 correlation¹⁸ analysis was restricted to the ~1 million variants included in HapMap 3 with MAF > 1% and imputation quality score $R^2 > 0.3$ 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 variant (**Supplementary Note**).

Genetic variance explained by identified susceptibility variants 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 variants, 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 variant, β_m is the true log odds ratio for the m th variant and M are the total number of causal variants among the GWAS variants. Thus, the proportion of heritability explained by identified variants relative to all imputable variants 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 disease³⁴. Under the frailty scale, we define the broad sense heritability³⁵ as σ^2 . The relationship between λ and σ^2 was shown to be $\sigma^2 = 2 * \log(\lambda)$ ³⁴. We assumed $\lambda = 2$ as the overall familial relative risk of invasive breast cancer³⁴, thus $\sigma^2 = 2\log(2)$ and the proportion of the familial relative risk explained by identified susceptibility variants 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**). In addition, we compared estimates of GWAS chip heritability across five-intrinsic subtypes using LD-score regression where the summary statistics were derived using either standard polytomous model applied to complete cases or the novel two-stage method that incorporates cases with missing tumor characteristics.

PRSs for five intrinsic-like subtypes

We constructed PRSs for the intrinsic-like subtypes, incorporating the newly identified variants and 313 variants previously reported in the development of PRSs for overall and ER-specific breast cancer²². The 313 SNPs include SNPs that didn't reach genome-wide significance. After excluding variants within 500 kb of the 313 SNPs or $LD \geq 0.1$, 17 out of the 32 novel variants were independent with the 313 SNPs. The BCAC data were split into the training dataset and test dataset with a proportion of 80%

and 20%, respectively. Half of the test dataset were five studies nested within prospective cohorts including KARMA, MMHS, PLCO, SISTER, UKBGS (**Supplementary Table 2**) and the other half was randomly selected among the subjects in OncoArray, excluding studies of bilateral breast cancer, studies or sub studies with oversampling for family history, cases with ambiguous diagnosis, and cases with missing tumor characteristics. We obtained the overall and ER-specific log odds ratios for 313 SNPs by respectively fitting standard and ER-specific logistic regression on the training dataset. We obtained the log odds ratio for 330 SNPs by fitting the fixed-effect two-stage polytomous model for five intrinsic-like subtypes on the training dataset (**Supplementary Table 19**).

Reporting Summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data Availability Statement

Summary level statistics are available from

<http://bcac.ccge.medschl.cam.ac.uk/bcacdata/> and

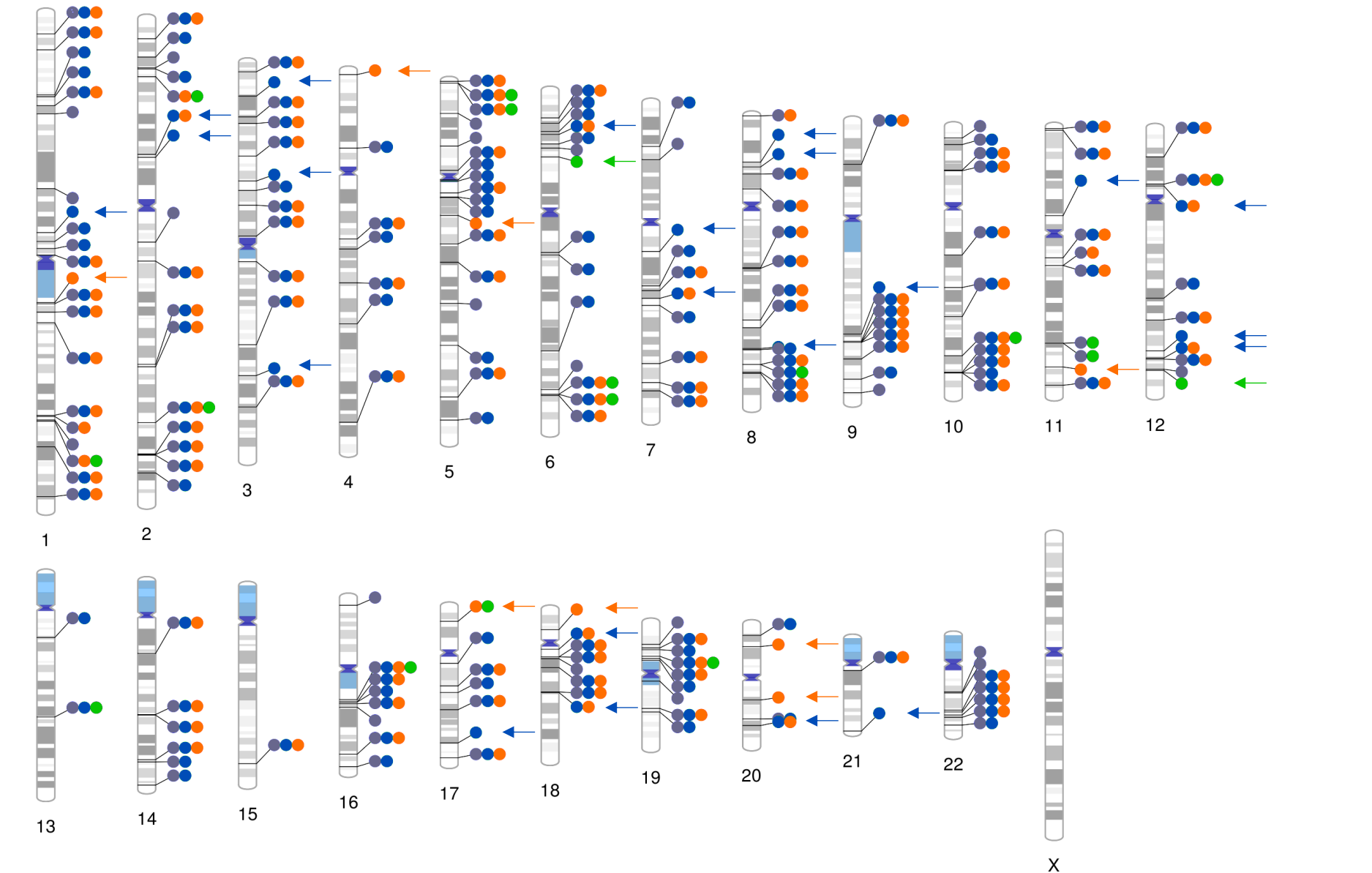
<http://cimba.ccge.medschl.cam.ac.uk/projects/>. Requests for data can be made to the corresponding author or the Data Access Coordination Committees (DACCs) of BCAC (see above URL) and CIMBA (see above URL). BCAC DACC approval is required to access data from the ABCFS, ABCS, ABCTB, BBCC, BBCS, BCEES, BCFR-NY, BCFR-PA, BCFR-UT, BCINIS, BSUCH, CBCS, CECILE, CGPS, CTS, DIETCOMPLYF, ESTHER, GC-HBOC, GENICA, GEPARSIXTO, GESBC, HABCS, HCSC, HEBCS, HMBCS, HUBCS, KARBAC, KBCP, LMBC, MABCS, MARIE, MBCSG, MCBBCS, MISS, MMHS, MTLGEBBCS, NC-BCFR, OFBCR, ORIGO, pKARMA, POSH, PREFACE, RBCS, SKKDKFZS, SUCCESSB, SUCCESSC, SZBCS, TNBCC, UCIBCS, UKBGS and UKOPS studies (**Supplementary Table 1**). CIMBA DACC approval is required to access data from the BCFR-ON, CONSIT TEAM, DKFZ, EMBRACE, FPGMX, GC-HBOC, GEMO, G-FAST, HEBCS, HEBON, IHCC, INHERIT, IOVHBOCS, IPOBCS, MCGILL, MODSQUAD, NAROD, OCGN, OUH and UKGRFOCR studies (**Supplementary Table 3**).

Code Availability statement

The data analysis code of this paper is available at https://github.com/andrewhaoyu/breast_cancer_data_analysis. The implementation of this two-stage polytomous regression method is available in a R package called TOP (<https://github.com/andrewhaoyu/TOP>) with a detailed tutorial available at <https://github.com/andrewhaoyu/TOP/blob/master/inst/TOP.pdf>.

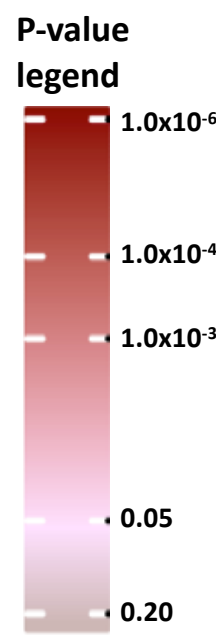
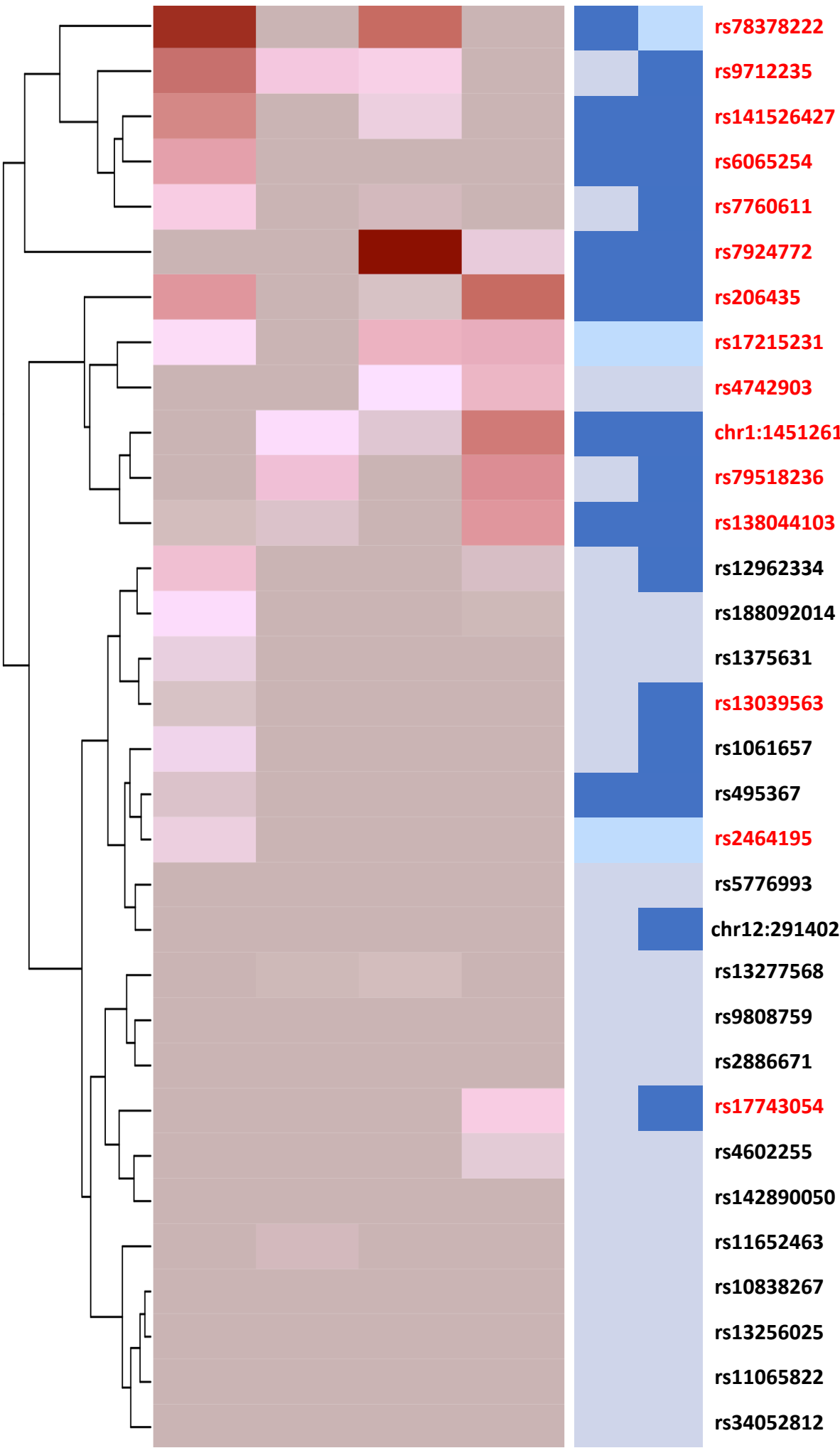
Methods-only references


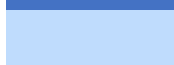
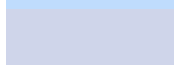


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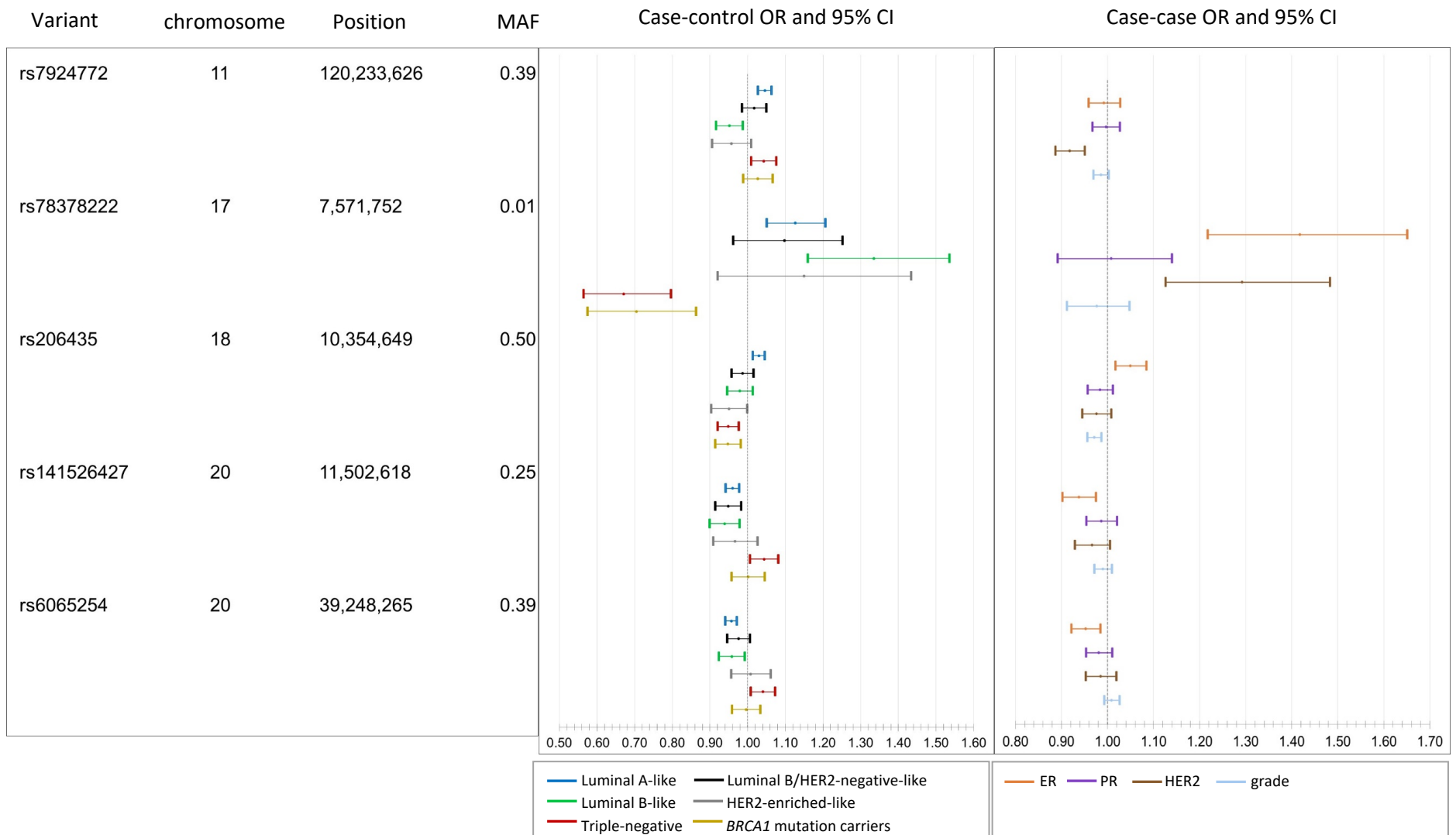


- Known variants
- Significant variants in overall analysis
- ← Overall analysis identified 22 novel variants
- ← Subtypes analysis identified 8 novel variants
- Significant variants in subtypes analysis
- Significant variants in BCAC TN and CIMBA *BRCA1* carriers meta-analysis
- ← BCAC TN and CIMBA *BRCA1* carriers meta-analysis identified 2 novel variants

ER PR HER2 Grade



-  Significant in two-stage polytomous regression
-  Significant in BCAC TN and CIMBA *BRCA1* meta analysis
-  Significant in Standard logistic regression
-  Significant in both two-stage polytomous regression and BCAC TN and CIMBA *BRCA1* meta analysis
-  Significant in both standard logistic regression and two-stage polytomous regression



1 Per-minor allele odds ratio and 95% confidence limits

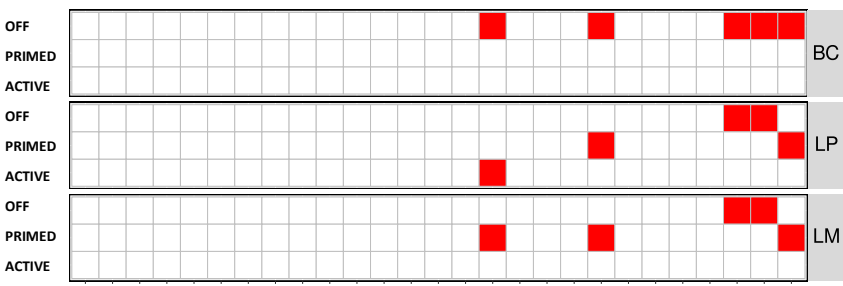
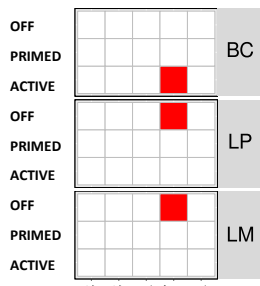
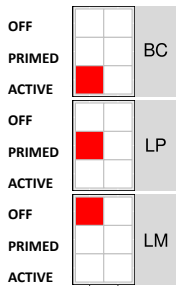
2 luminal A-like (ER+ and/or PR+, HER2-, grade 1 & 2); luminal B/HER2-negative-like (ER+ and/or PR+, HER2-, grade 3); luminal B-like (ER+ and/or PR+, HER2+); (4) HER2-enriched-like (ER- and PR-, HER2+), and triple-negative (ER-, PR-, HER2-)

a) Lead SNP: rs78378222
 CHR: 17
 Position: 7,571,752

b) Lead SNP: rs141526427
 CHR: 20
 Position: 11,502,618

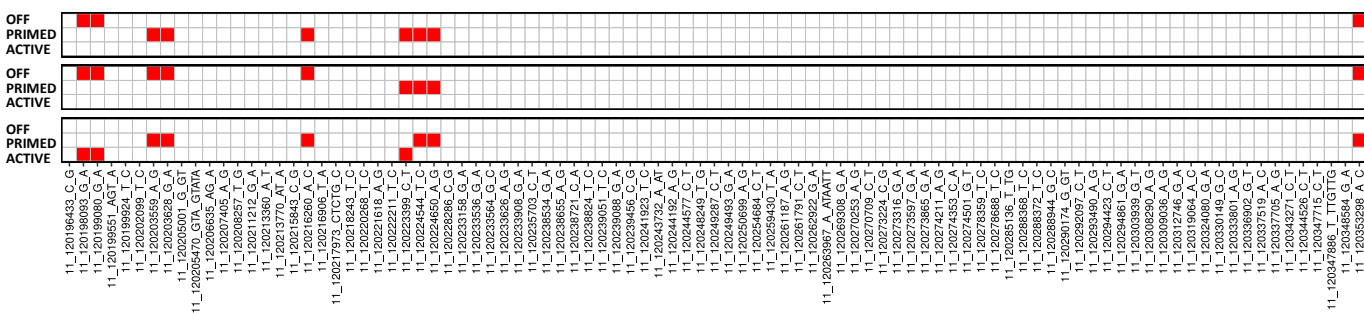
c) Lead SNP: rs605254
 CHR: 20
 Position: 39,248,265

Enhancer state



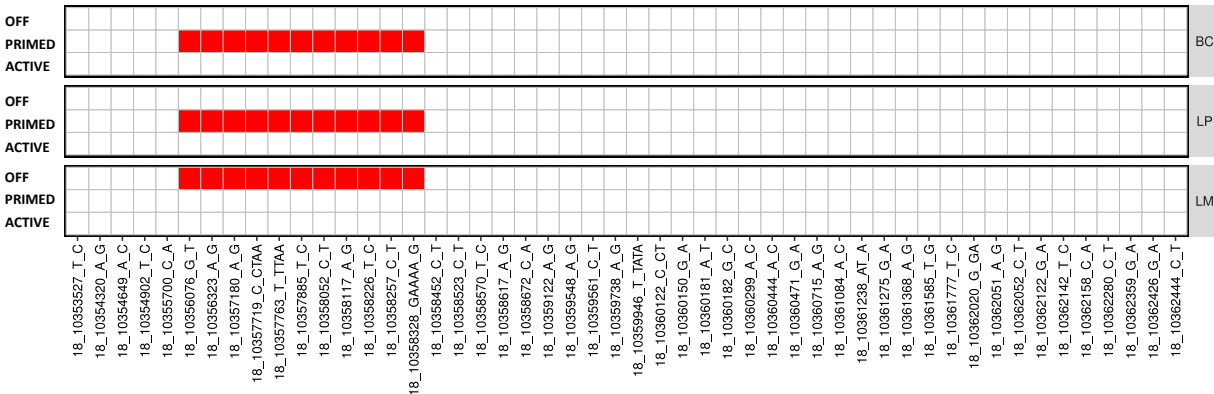
d) Lead SNP: rs7924772
 CHR: 11
 Position: 120,233,626

Enhancer state

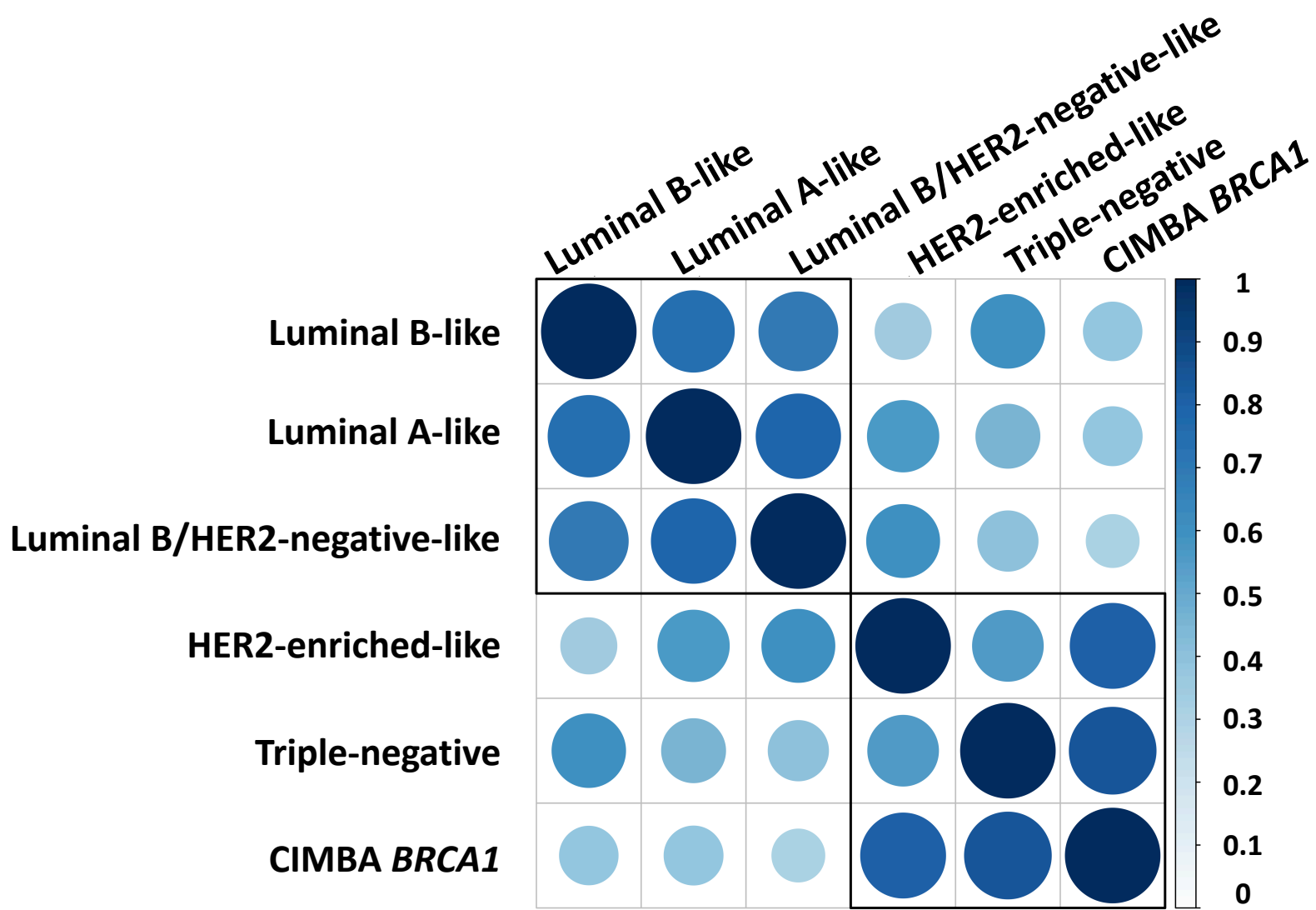


e) Lead SNP: rs2064335
 CHR: 18
 Position: 10,354,649

Enhancer state

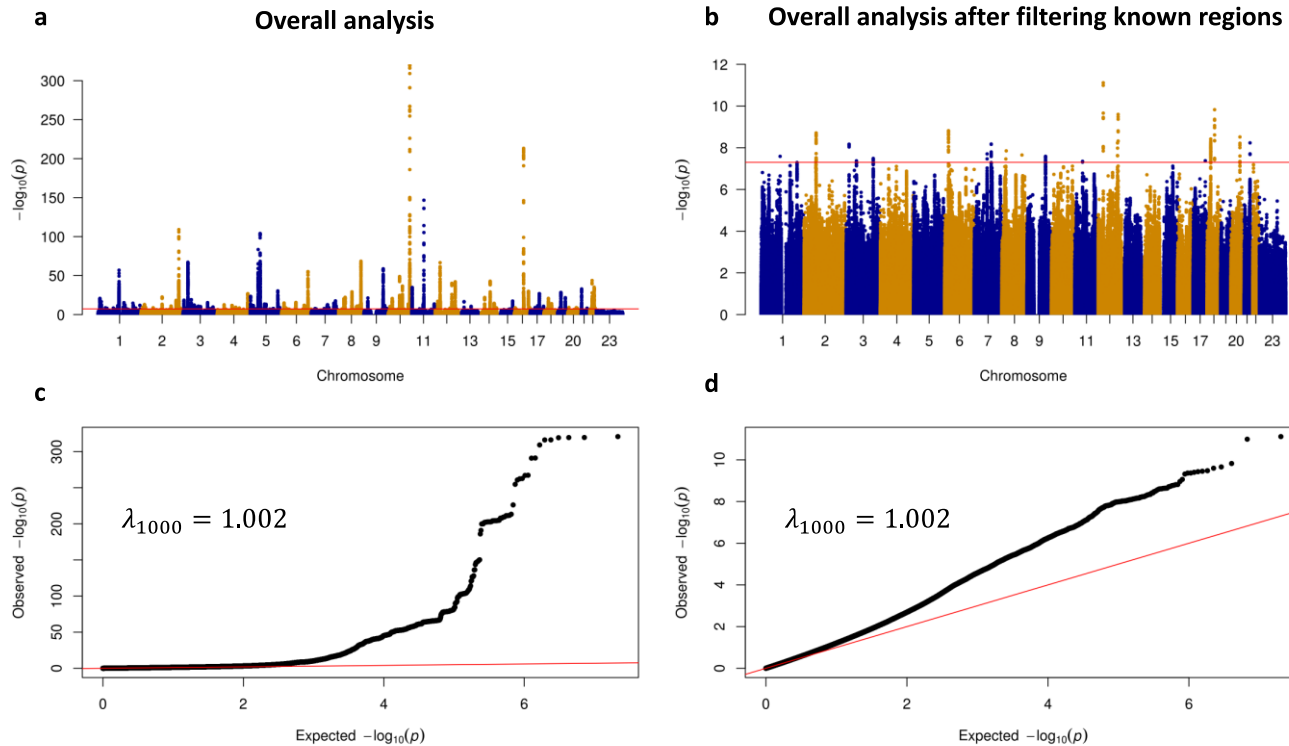


Candidate causal variants (CCVs)



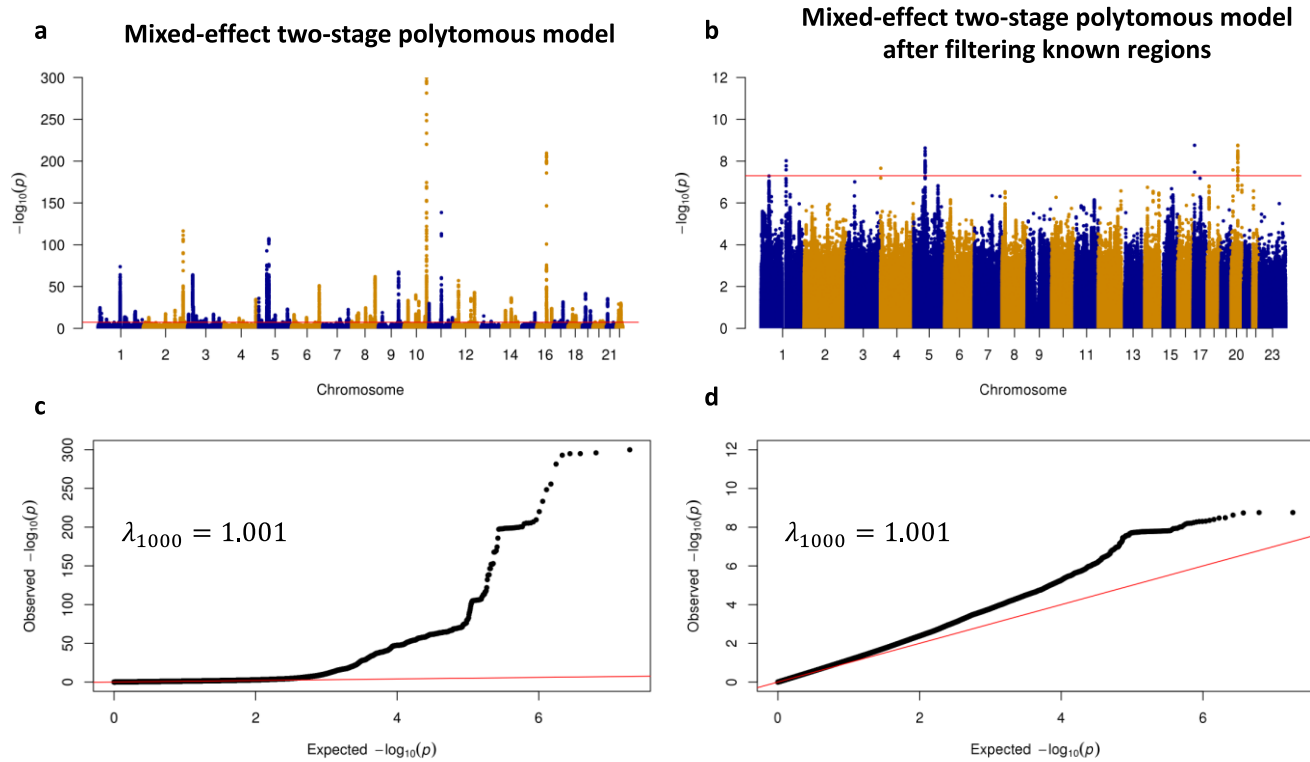
Supplementary figure 1. Variants associations with overall breast cancer risk identified using standard logistic regression ($n = 133,384$ cases, $n = 113,789$ controls). **a)** Manhattan plot showing $-\log_{10}P$ values for variant associations with breast cancer risk. **b)** Manhattan plot after excluding previous known regions (Online Methods) **c)** Quantile-Quantile (Q-Q) plot of observed P-values versus expected P-values for all variants. **d)** QQ plot¹ after excluding previous known regions. P-values are raw p-values from two-tailed z-test statistics. Bonferroni correction was used to account for multiple testing (cut off P-value = 5×10^{-8}).

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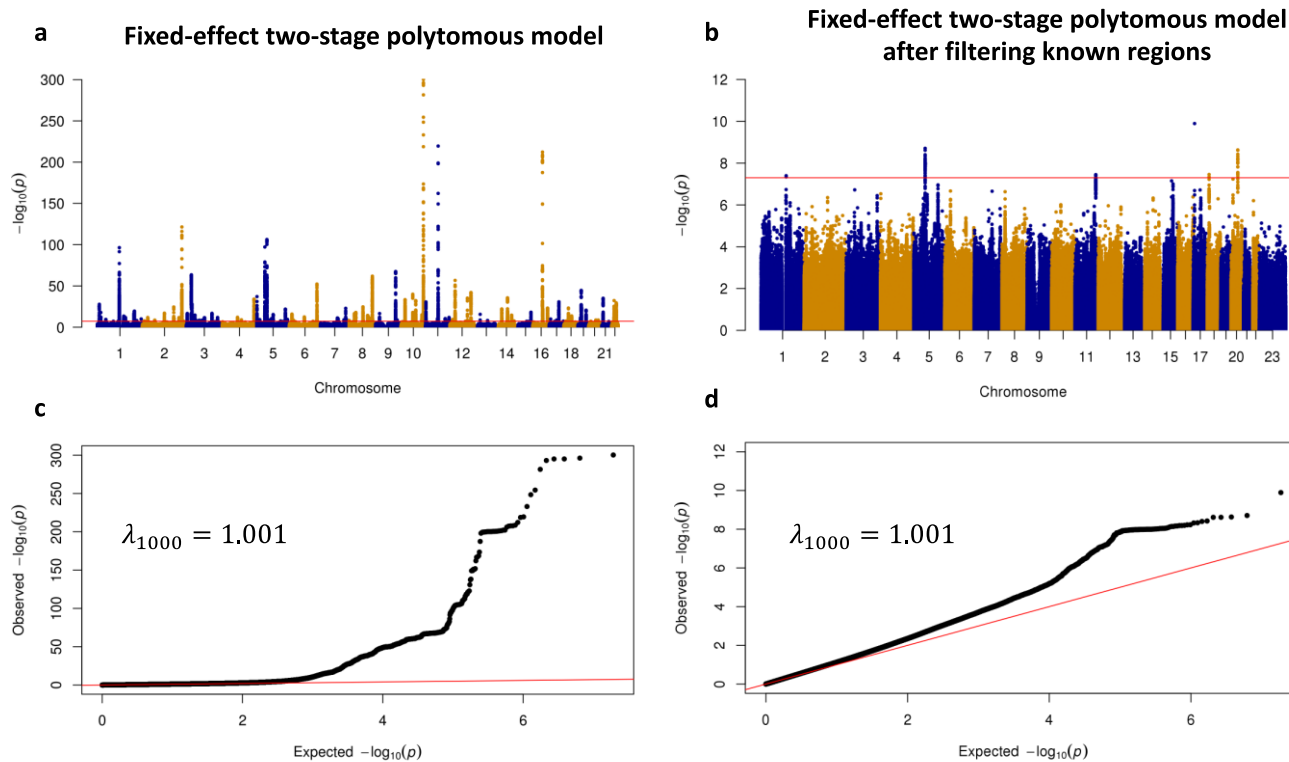
1) λ_{1000} scale the genomic inflation factor λ to a study with sample size of 1000 cases and 1000 controls using the formula $\lambda_{1000} = 1 + 500 * (\lambda - 1) / (\frac{1}{n_{cases}} + \frac{1}{n_{control}})$

Supplementary figure 2. Variant associations with breast cancer risk using a mixed-effect two-stage model (**Oline Methods**) accounting for tumor heterogeneity according to the ER, PR, HER2, and grade (**n = 106,278 invasive cases, n = 91,477 controls**). **a)** Manhattan plot showing $-\log_{10}P$ values for variant associations with breast cancer risk. **b)** Manhattan plot showing $-\log_{10}P$ values for variant associations with breast cancer risk after excluding previously known regions (Online Methods) and 22 loci identified through standard logistic regression analysis (**Supplementary Figure 2**). **c)** QQ plot¹ of observed P-values versus expected P-values for all variants. **d)** QQ plot of observed P-values versus expected P-values for remaining variants after excluding previously known regions and 22 loci identified through standard logistic regression analysis. P-values are raw p-values from two-tailed z-test statistics. Bonferroni correction was used to account for multiple testing (cut off P-value = 5×10^{-8}).



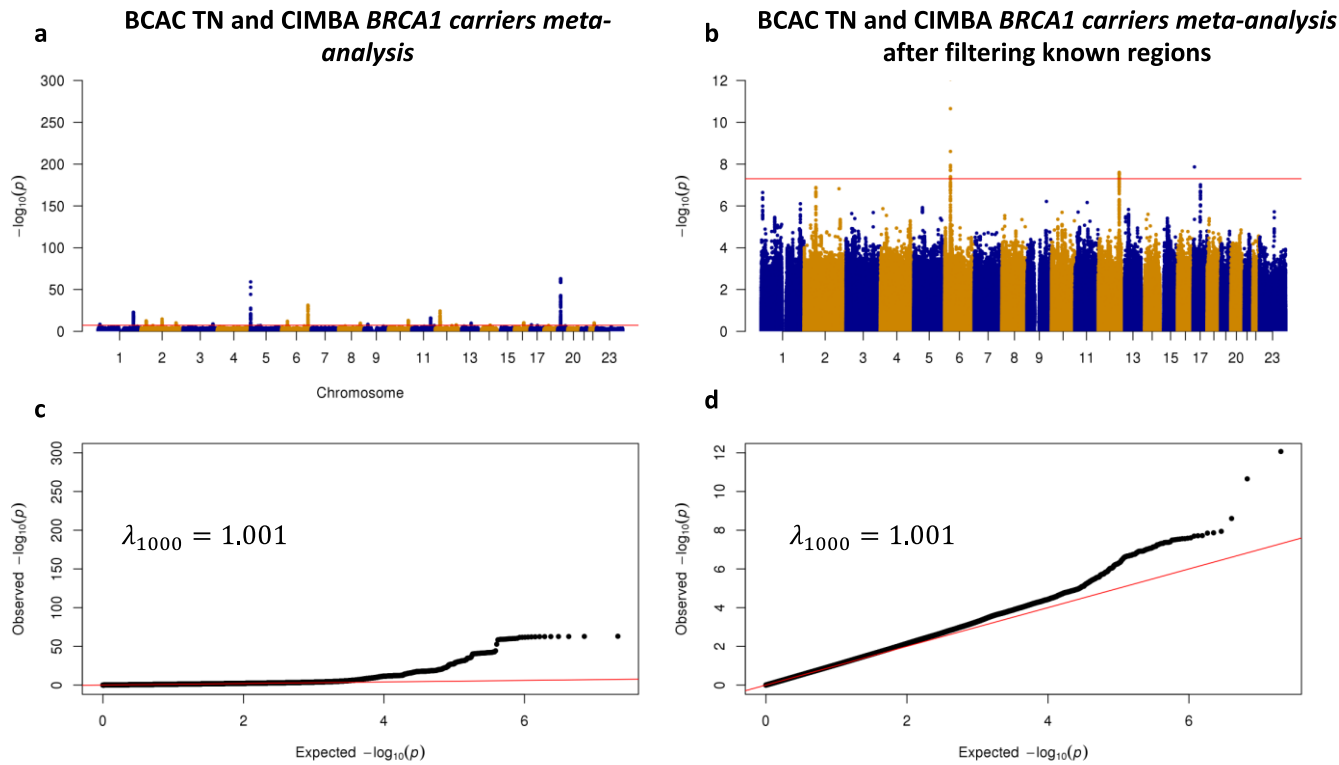
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Supplementary figure 3. Variant associations with breast cancer risk using a fixed-effect two-stage model (**Oline Methods**) accounting for tumor heterogeneity according to the ER, PR, HER2, and grade (**n = 106,278 invasive cases, n = 91,477 controls**). **a)** Manhattan plot showing $-\log_{10}P$ values for variant associations with breast cancer risk. **b)** Manhattan plot showing $-\log_{10}P$ values for variant associations with breast cancer risk after excluding previously known regions (Online Methods) and 22 loci identified through standard logistic regression analysis (**Supplementary Figure 2**). **c)** QQ plot¹ of observed P-values versus expected P-values for all variants. **d)** QQ plot of observed P-values versus expected P-values for remaining variants after excluding previously known regions and 22 loci identified through standard analysis. P-values are raw p-values from two-tailed z-test statistics. Bonferroni correction was used to account for multiple testing (cut off P-value = 5×10^{-8}).



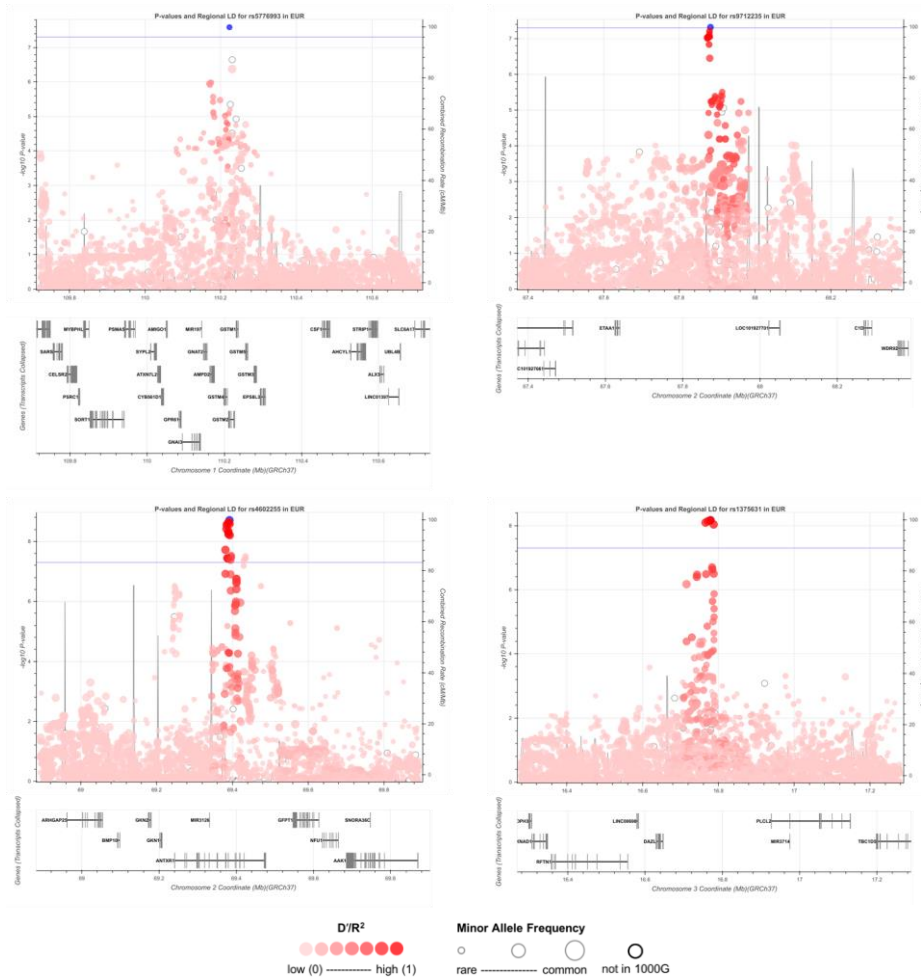
1) λ_{1000} scale the genomic inflation factor λ to a study with sample size of 1000 cases and 1000 controls using the formula $\lambda_{1000} = 1 + 500 * (\lambda - 1) / (\frac{1}{n_{cases}} + \frac{1}{n_{control}})$

Supplementary figure 4. Variant association with triple-negative (TN) breast cancer risk using a fixed-effect meta-analysis of results between BCAC TN and CIMBA *BRCA1* carriers (BCAC: n = 8,602 effective triple-negative cases, n = 91,477 controls; CIMBA *BRCA1* carriers: n = 9,414 cases, n = 9,494 controls). **a)** Manhattan plot showing $-\log_{10}P$ values for variant associations with triple-negative TN breast cancer risk. **b)** Manhattan plot showing $-\log_{10}P$ values for variant associations with triple-negative TN breast cancer risk after excluding previously known regions (Online Methods). **c)** QQ plot¹ of observed P-values versus expected P-values for all variants **d)** QQ plot of observed P-values versus expected P-values for remaining variants after excluding previously known regions. P-values are raw p-values from two-tailed z-test statistics. Bonferroni correction was used to account for multiple testing (cut off P-value = 5×10^{-8}).

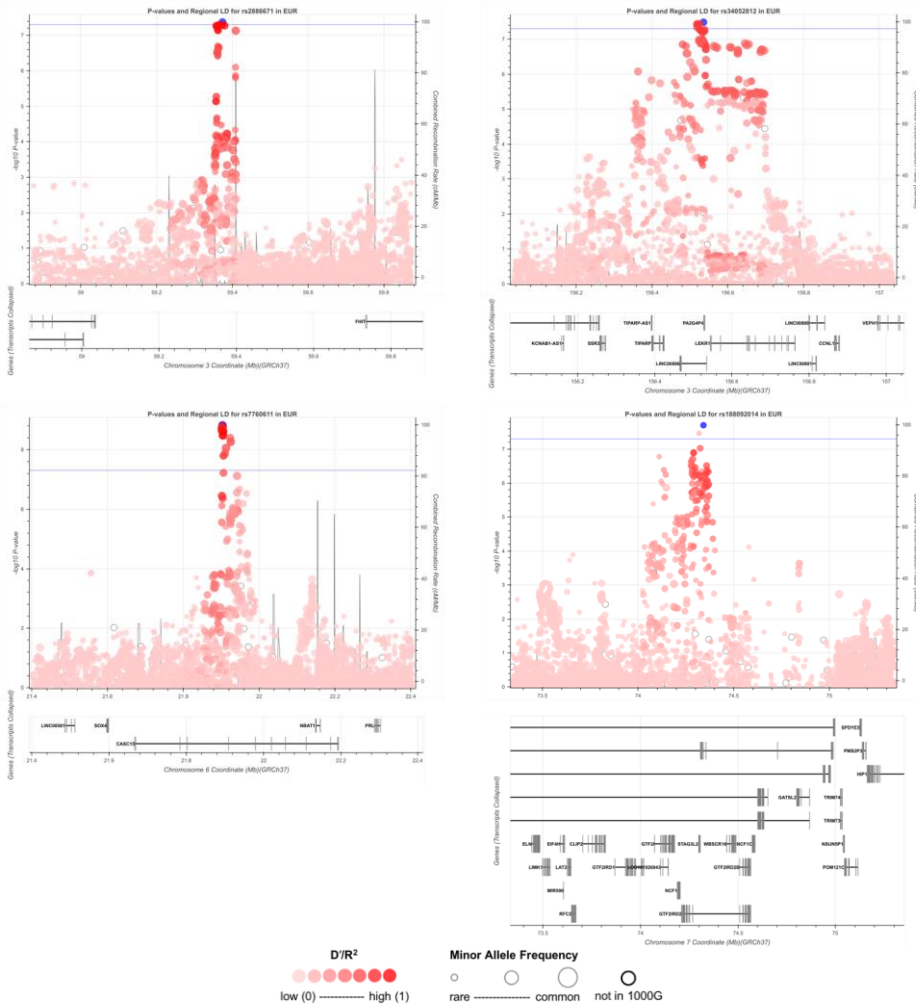


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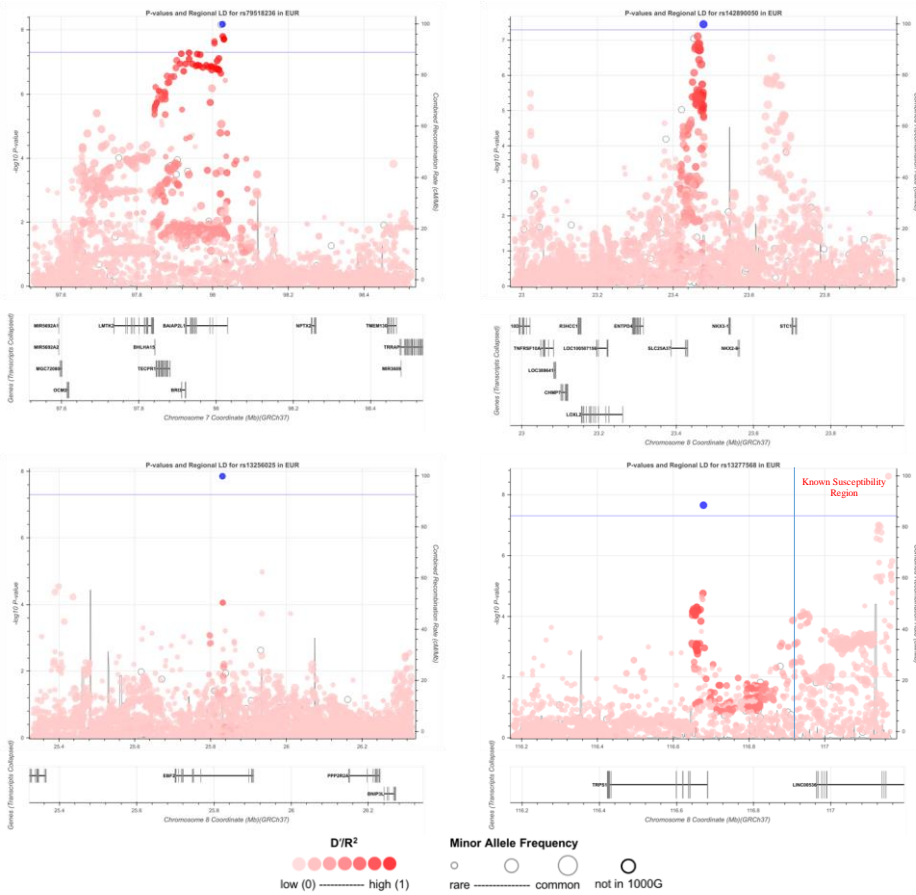
Supplementary figure 5. Regional plots of the 32 identified breast cancer variants. The first 22 variants were identified through standard logistic regression ($n = 133,384$ cases, $n = 113,789$ controls), the following eight variants were identified through two-stage polytomous regression ($n = 106,278$ invasive cases, $n = 91,477$ controls), the last two variants were identified through meta-analysis of BCAC triple-negative TN and CIMBA *BRCA1* carriers (BCAC: $n = 8,602$ effective triple-negative cases, $n = 91,477$ controls; CIMBA *BRCA1* carriers: $n = 9,414$ cases, $n = 9,494$ controls). Plotted area is showing ± 500 KB region around the identified susceptibility variant. P-values are raw p-values from two-tailed z-test statistics. Bonferroni correction was used to account for multiple testing (cut off P-value = 5×10^{-8}).



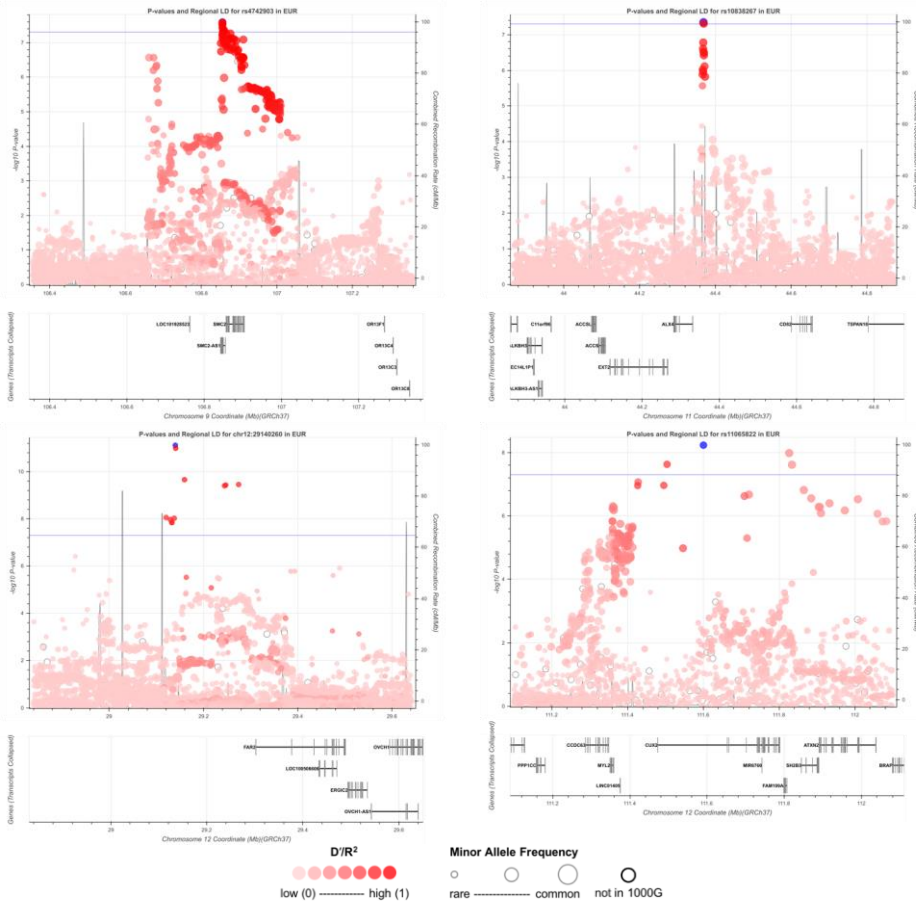
Supplementary figure 5 continued. Regional plots of the 32 identified breast cancer variants. The first 22 variants were identified through standard logistic regression ($n = 133,384$ cases, $n = 113,789$ controls), the following eight variants were identified through two-stage polytomous regression ($n = 106,278$ invasive cases, $n = 91,477$ controls), the last two variants were identified through meta-analysis of BCAC triple-negative and CIMBA *BRCA1* carriers (BCAC: $n = 8,602$ effective triple-negative cases, $n = 91,477$ controls; CIMBA *BRCA1* carriers: $n = 9,414$ cases, $n = 9,494$ controls). Plotted area is showing ± 500 KB region around the identified susceptibility variant. P-values are raw p-values from two-tailed z-test statistics. Bonferroni correction was used to account for multiple testing (cut off P-value = 5×10^{-8}).



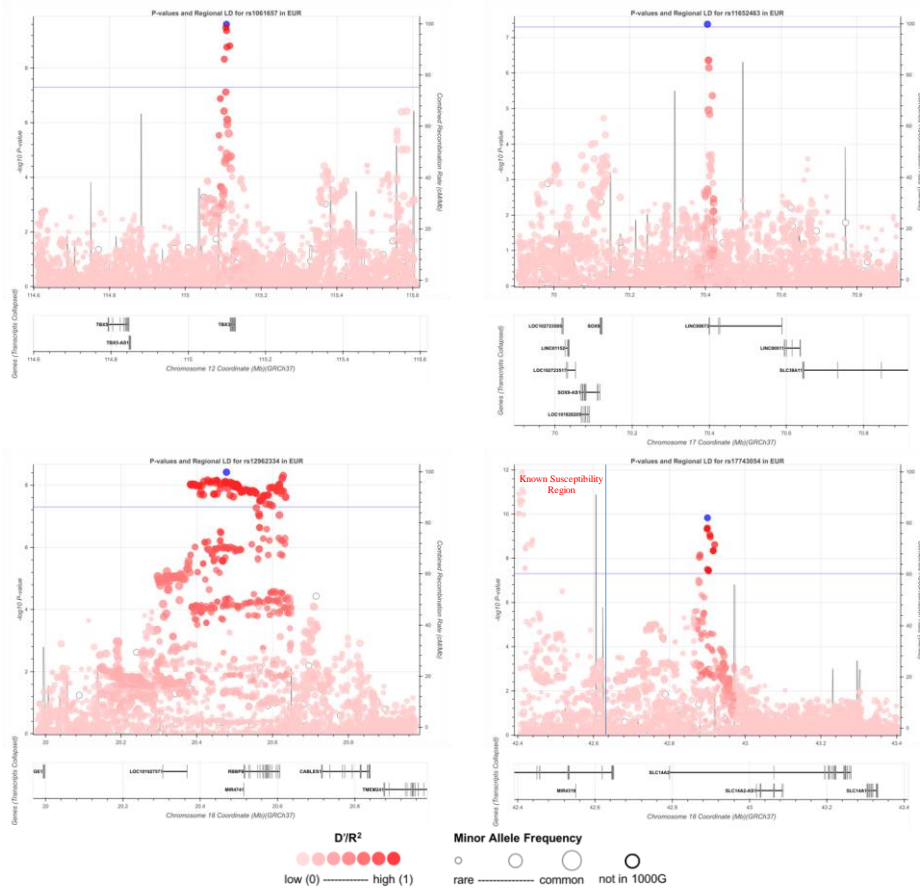
Supplementary figure 5 continued. Regional plots of the 32 identified breast cancer variants. The first 22 variants were identified through standard logistic regression ($n = 133,384$ cases, $n = 113,789$ controls), the following eight variants were identified through two-stage polytomous regression ($n = 106,278$ invasive cases, $n = 91,477$ controls), the last two variants were identified through meta-analysis of BCAC triple-negative and CIMBA *BRCA1* carriers (BCAC: $n = 8,602$ effective triple-negative cases, $n = 91,477$ controls; CIMBA *BRCA1* carriers: $n = 9,414$ cases, $n = 9,494$ controls). Plotted area is showing ± 500 KB region around the identified susceptibility variant. P-values are raw p-values from two-tailed z-test statistics. Bonferroni correction was used to account for multiple testing (cut off P-value = 5×10^{-8}).



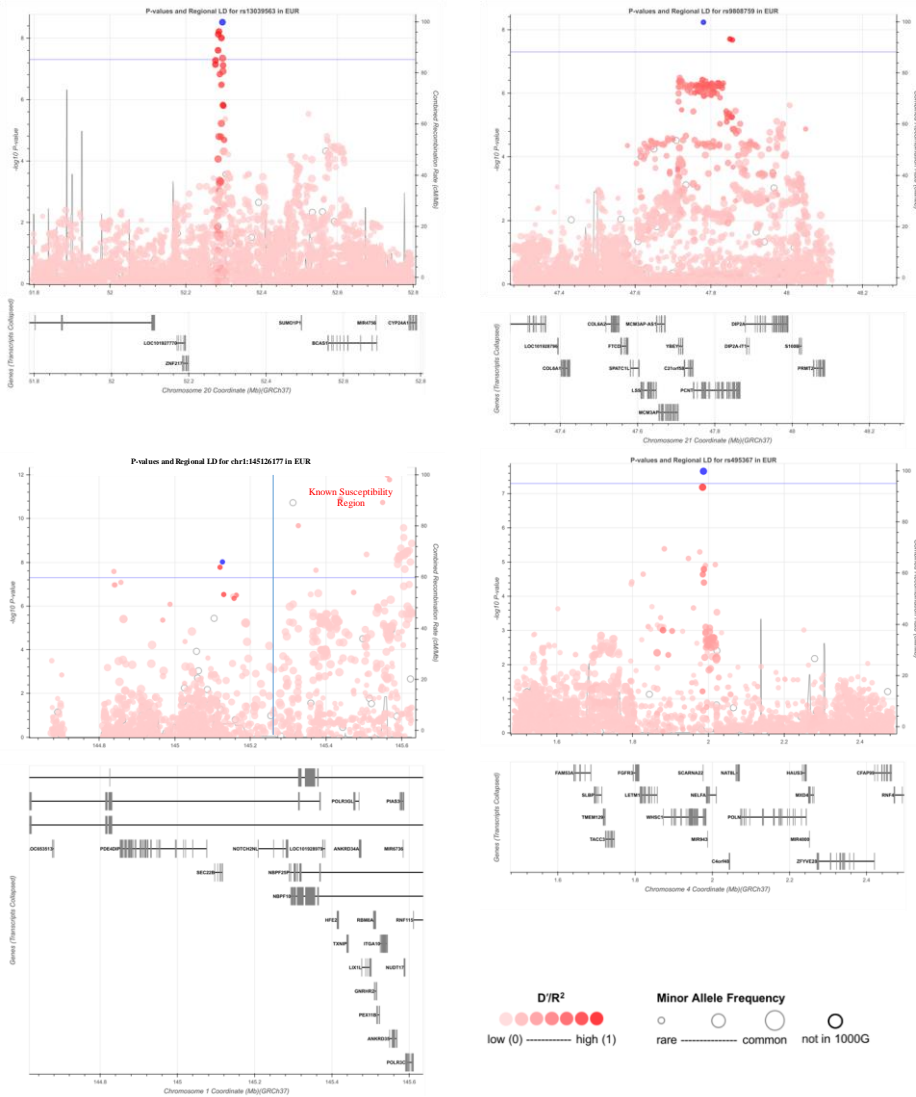
Supplementary figure 5 continued. Regional plots of the 32 identified breast cancer variants. The first 22 variants were identified through standard logistic regression ($n = 133,384$ cases, $n = 113,789$ controls), the following eight variants were identified through two-stage polytomous regression ($n = 106,278$ invasive cases, $n = 91,477$ controls), the last two variants were identified through meta-analysis of BCAC triple-negative and CIMBA *BRCA1* carriers (BCAC: $n = 8,602$ effective triple-negative cases, $n = 91,477$ controls; CIMBA *BRCA1* carriers: $n = 9,414$ cases, $n = 9,494$ controls). Plotted area is showing ± 500 KB region around the identified susceptibility variant. P-values are raw p-values from two-tailed z-test statistics. Bonferroni correction was used to account for multiple testing (cut off P-value = 5×10^{-8}).



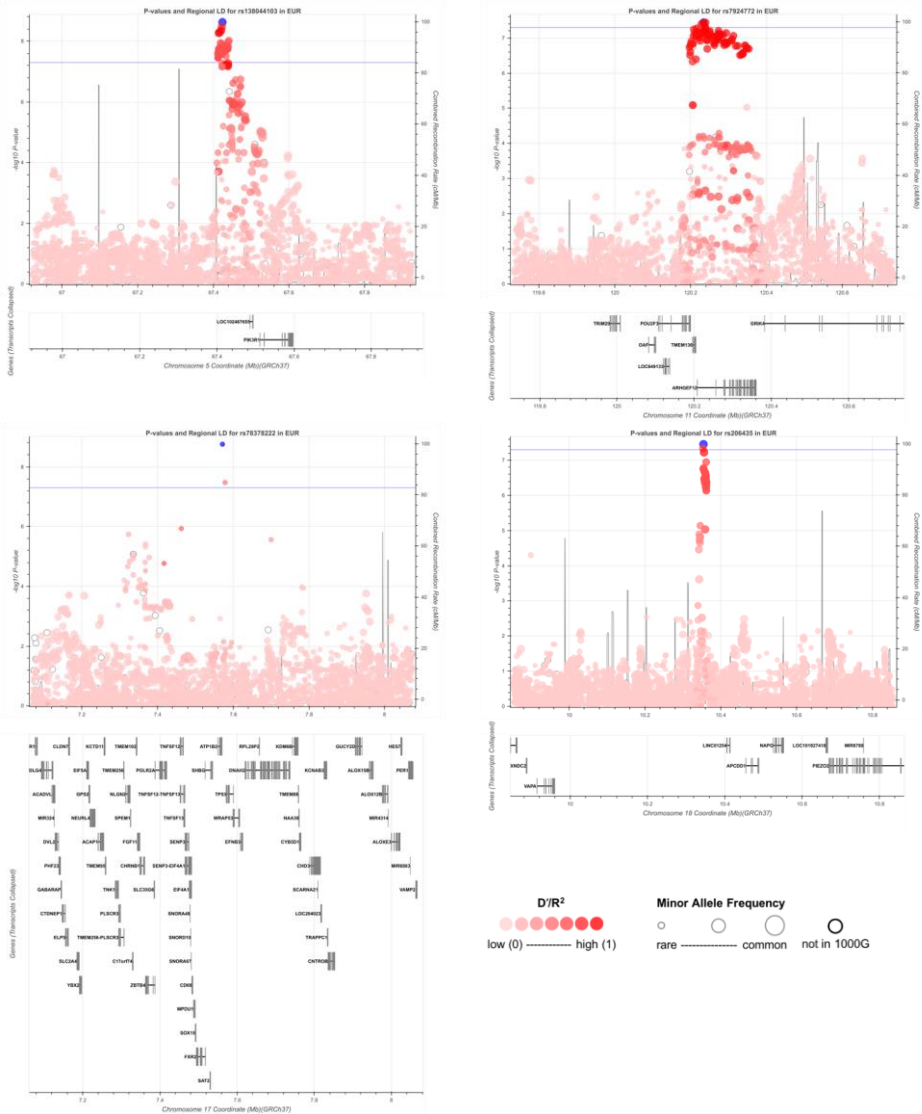
Supplementary figure 5 continued. Regional plots of the 32 identified breast cancer variants. The first 22 variants were identified through standard logistic regression (n = 133,384 cases, n = 113,789 controls), the following eight variants were identified through two-stage polytomous regression (n = 106,278 invasive cases, n = 91,477 controls), the last two variants were identified through meta-analysis of BCAC triple-negative and CIMBA *BRCA1* carriers (BCAC: n = 8,602 effective triple-negative cases, n = 91,477 controls; CIMBA *BRCA1* carriers: n = 9,414 cases, n = 9,494 controls). Plotted area is showing ± 500 KB region around the identified susceptibility variant. P-values are raw p-values from two-tailed z-test statistics. Bonferroni correction was used to account for multiple testing (cut off P-value = 5×10^{-8}).



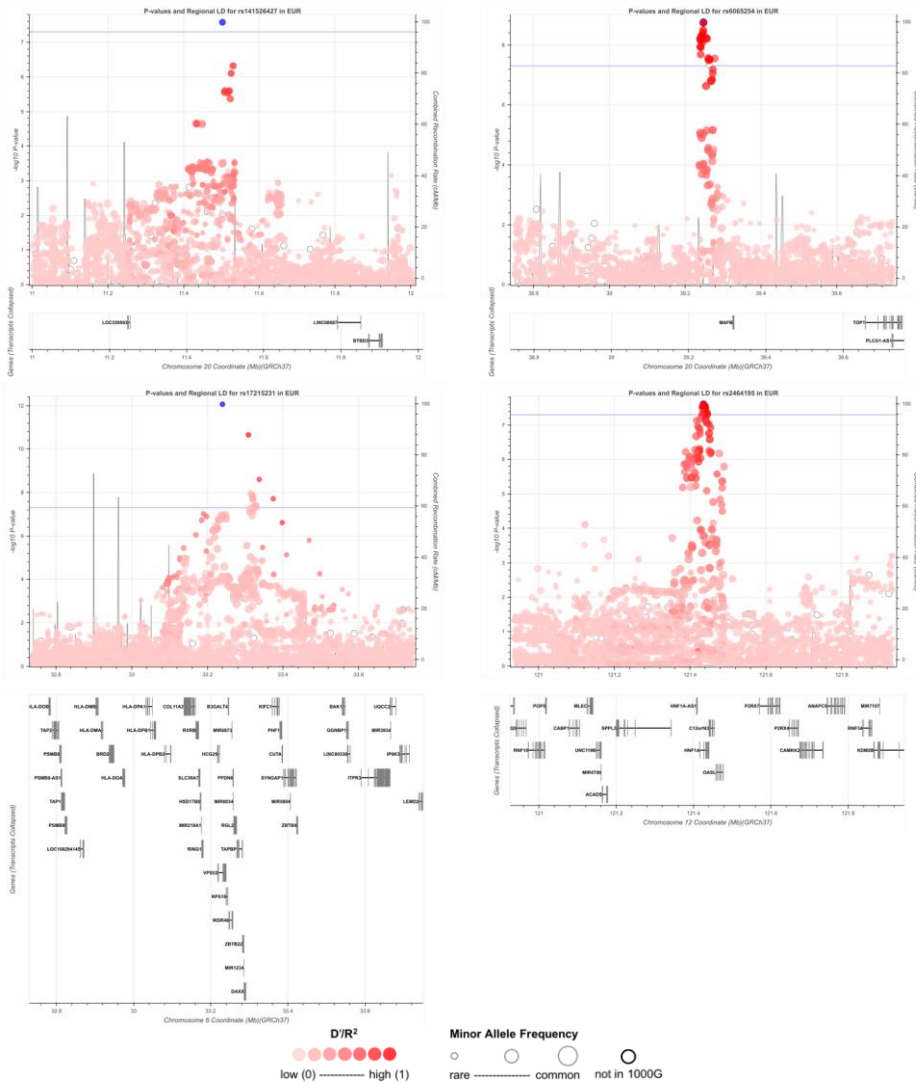
Supplementary figure 5 continued. Regional plots of the 32 identified breast cancer variants. The first 22 variants were identified through standard logistic regression ($n = 133,384$ cases, $n = 113,789$ controls), the following eight variants were identified through two-stage polytomous regression ($n = 106,278$ invasive cases, $n = 91,477$ controls), the last two variants were identified through meta-analysis of BCAC triple-negative and CIMBA *BRCA1* carriers (BCAC: $n = 8,602$ effective triple-negative cases, $n = 91,477$ controls; CIMBA *BRCA1* carriers: $n = 9,414$ cases, $n = 9,494$ controls). Plotted area is showing ± 500 KB region around the identified susceptibility variant. P-values are raw p-values from two-tailed z-test statistics. Bonferroni correction was used to account for multiple testing (cut off P-value = 5×10^{-8}).



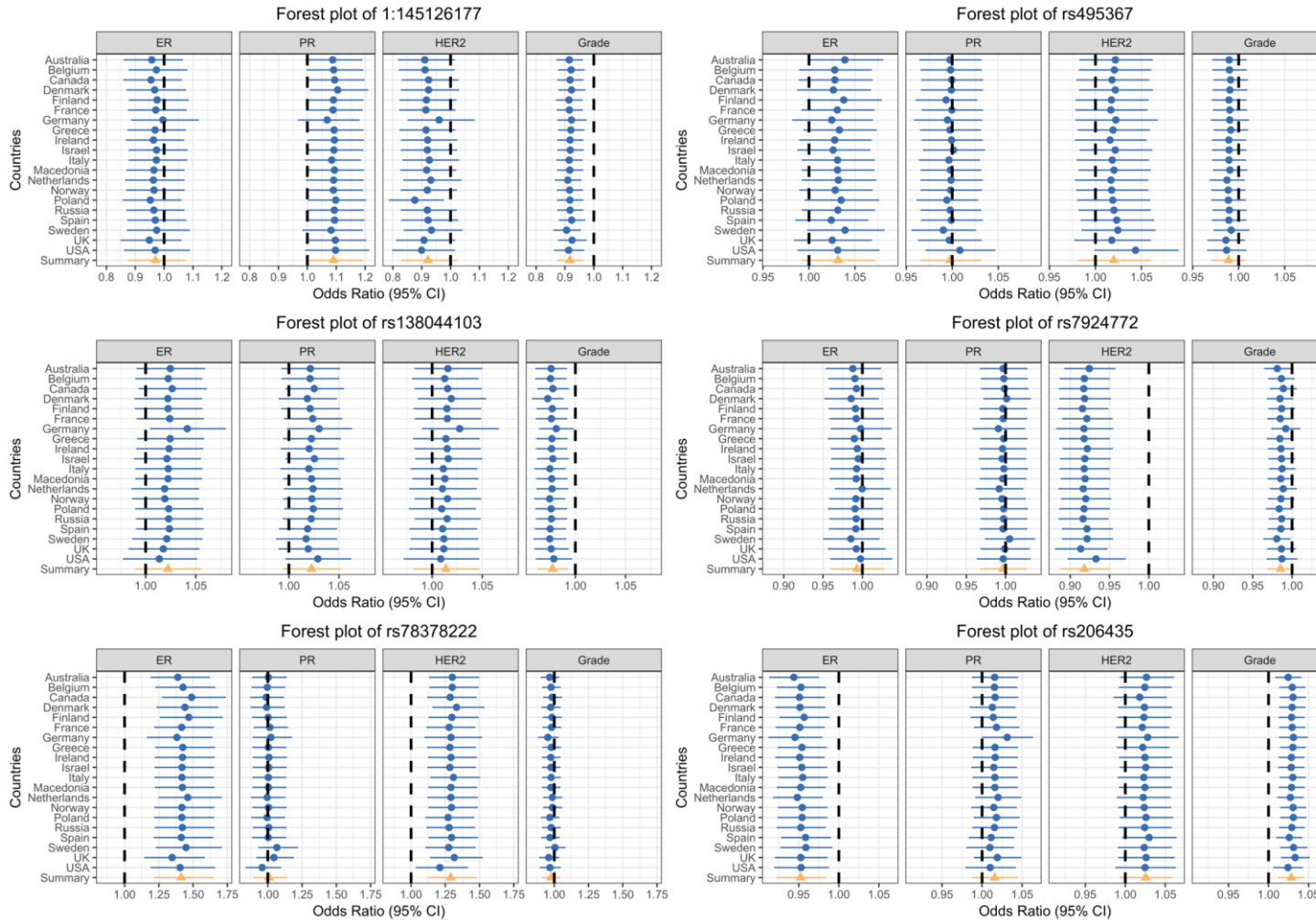
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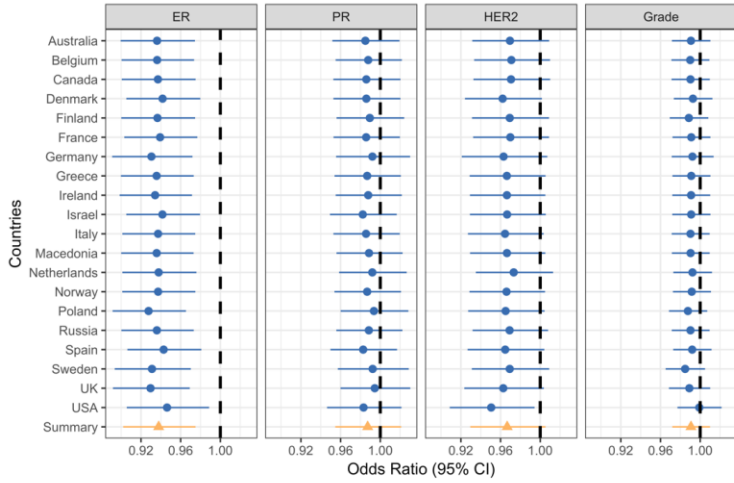
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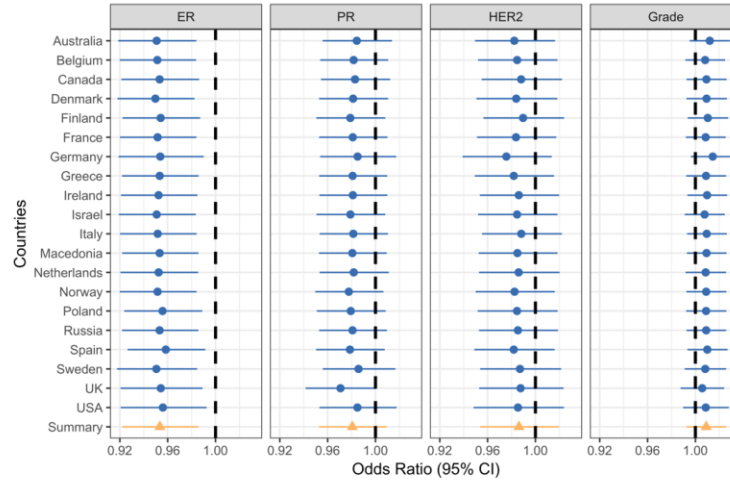
Supplementary figure 6. Country Specific sensitivity analysis of eight novel genome-wide significant loci identified using the two-stage regression models ($n = 106,278$ invasive cases, $n = 91,477$ controls), and chr22:40042814 which was dropped since the signal was observed only in studies from the USA.



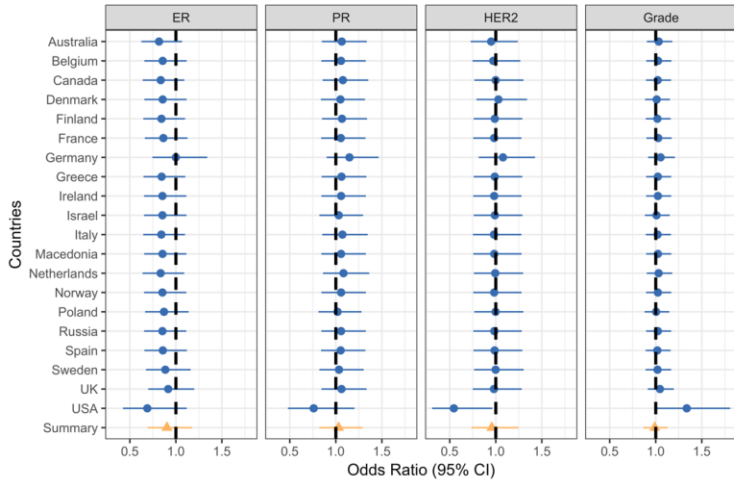
Forest plot of rs141526427



Forest plot of rs6065254



Forest plot of chr22_40042814_C_T



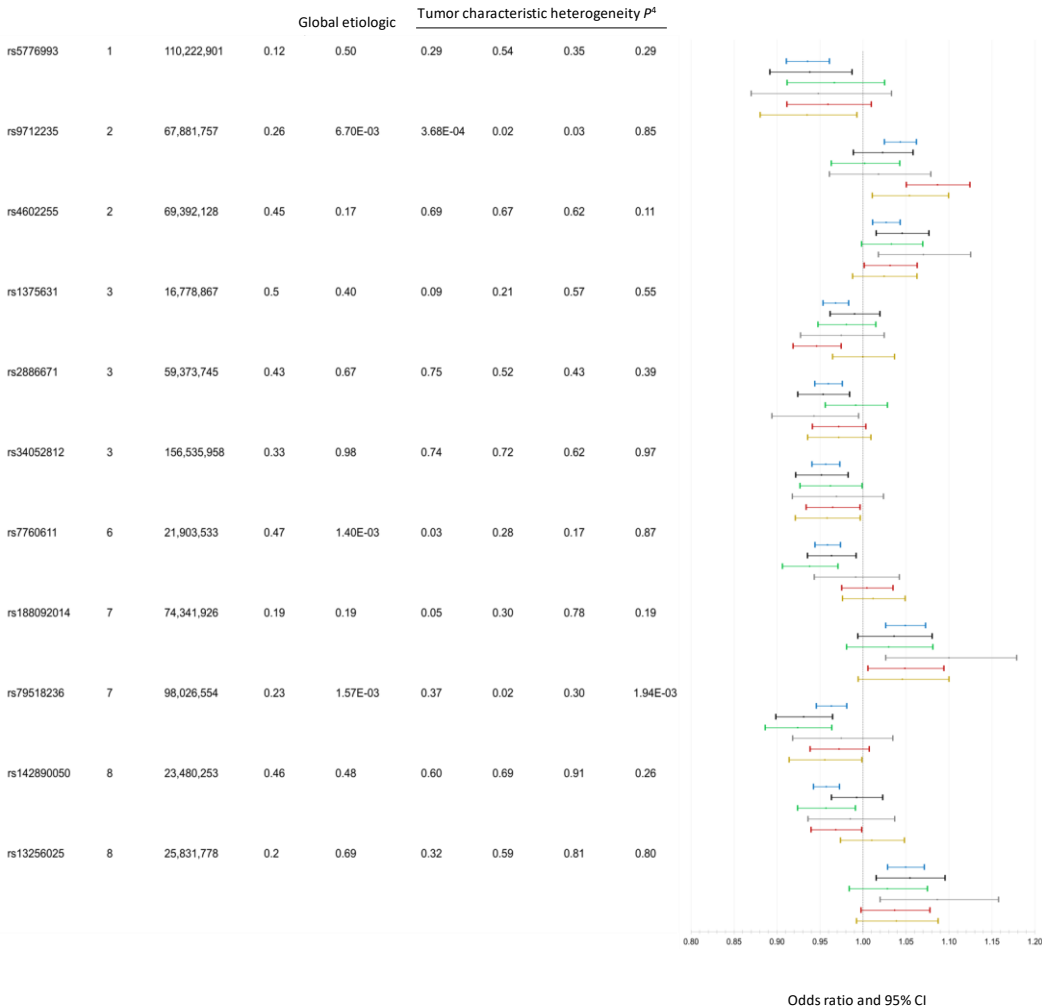
Supplementary Figure 7. Associations¹ between novel susceptibility variants identified using standard logistic regression with intrinsic-like breast cancer subtypes² (right panel, n = 106,278 invasive cases, n = 91,477 controls) and the second-stage heterogeneity p-values from the two-stage polytomous logistic regression model (left panel, n = 106,278 invasive cases, n = 91,477 controls).

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— Luminal A-like — Luminal B/HER2-negative-like — Luminal B-like — HER2-enriched-like — Triple-negative — BRCA1 mutation carriers

- 1 Per-minor allele odds ratio (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+); HER2-enriched-like (ER- and PR-, HER2+); triple-negative (ER-, PR-, HER2-)
3. Based on a mixed-effect two-stage polytomous model testing for heterogeneity between susceptibility variants and ER, PR, HER2, and grade, where ER was entered into the model as a fixed-effect term and PR, HER2, and grade were entered into the model as random-effect terms.
4. Results from second stage case-case parameters from a fixed effect two-stage polytomous model testing for heterogeneity between susceptibility variants and ER, PR, HER2, and grade, where ER, PR, HER2, and grade are mutually adjusted for each other
5. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2)

Supplementary Figure 7 continued. Associations¹ between novel susceptibility variants identified using standard logistic regression with intrinsic-like breast cancer subtypes² (right panel, n = 106,278 invasive cases, n = 91,477 controls) and the second-stage heterogeneity p-values from the two-stage polytomous logistic regression model (left panel, n = 106,278 invasive cases, n = 91,477 controls),

Associations³ between novel susceptibility variants identified using standard logistic regression with intrinsic-like breast cancer subtypes² (right panel) and the second-stage heterogeneity p-values from the two-stage polytomous logistic

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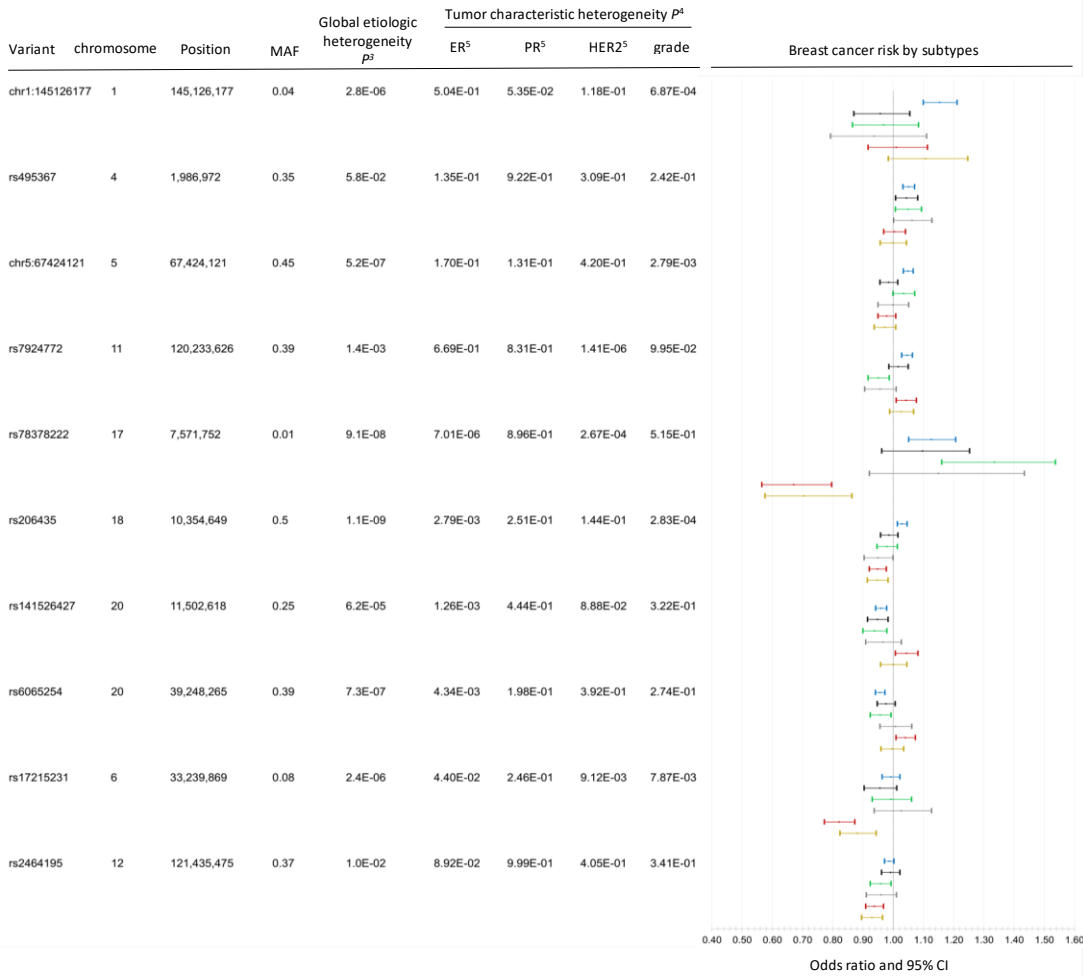


regression model (left panel)

Variant	chromosome	Position	MAF	Global etiologic heterogeneity p ²	Tumor characteristic heterogeneity P ⁴				Breast cancer risk by subtypes
					ER neg	PR pos	HER2 neg	grade 1-2	

- HER2-enriched-like (ER- and PR-, HER2+); triple-negative (ER-, PR-, HER2-)
- Based on a mixed-effect two-stage polytomous model testing for heterogeneity between susceptibility variants and ER, PR, HER2, and grade, where ER was entered into the model as a fixed-effect term and PR, HER2, and grade were entered into the model as random-effect terms.
 - Results from second stage case-case parameters from a fixed effect two-stage polytomous model testing for heterogeneity between susceptibility variants and ER, PR, HER2, and grade, where ER, PR, HER2, and grade are mutually adjusted for each other
 - Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2)

Supplementary Figure 8 Risk¹ of breast cancer subtypes defined by intrinsic-like subtypes² (n = 106,278 invasive cases, n = 91,477 controls) among loci identified using the two-stage polytomous logistic regression model and the CIMBA / BCAC triple-negative meta-analysis.



— Luminal A-like — Luminal B/HER2-negative-like — Luminal B-like — HER2-enriched-like — Triple-negative — BRCA1 mutation carriers

1 Per-minor allele odds ratio (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+); HER2-enriched-like (ER- and PR-, HER2+); triple-negative (ER-, PR-, HER2-)

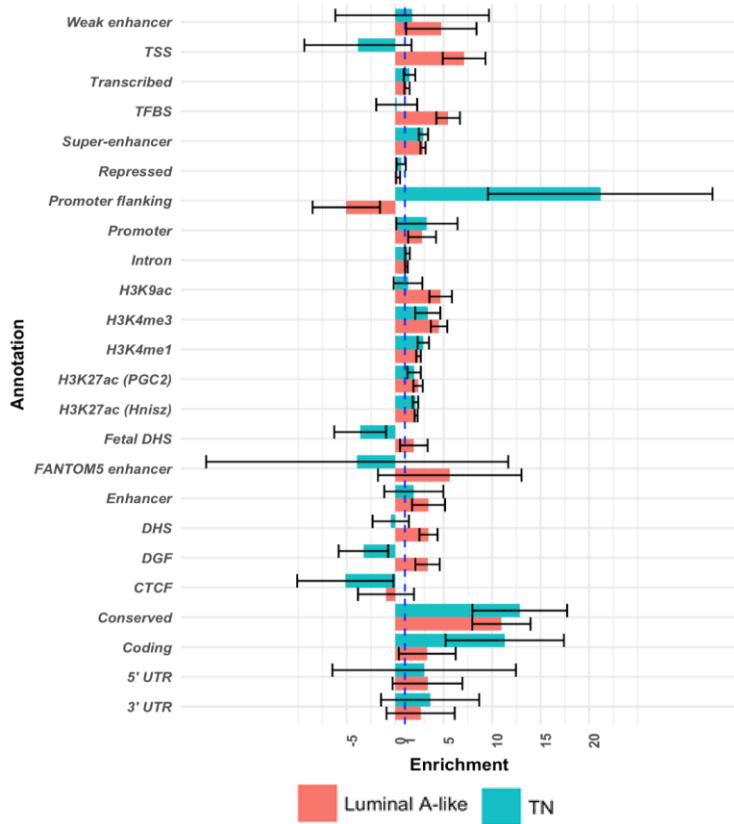
3. Based on a mixed-effect two-stage polytomous model testing for heterogeneity between susceptibility variants and ER, PR, HER2, and grade, where ER was entered into the model as a fixed-effect term and PR, HER2, and grade were entered into the model as random-effect terms.

4. Results from second stage case-case parameters from a fixed effect two-stage polytomous model testing for heterogeneity between susceptibility variants and ER, PR, HER2, and grade, where ER, PR, HER2, and grade are mutually adjusted for each other

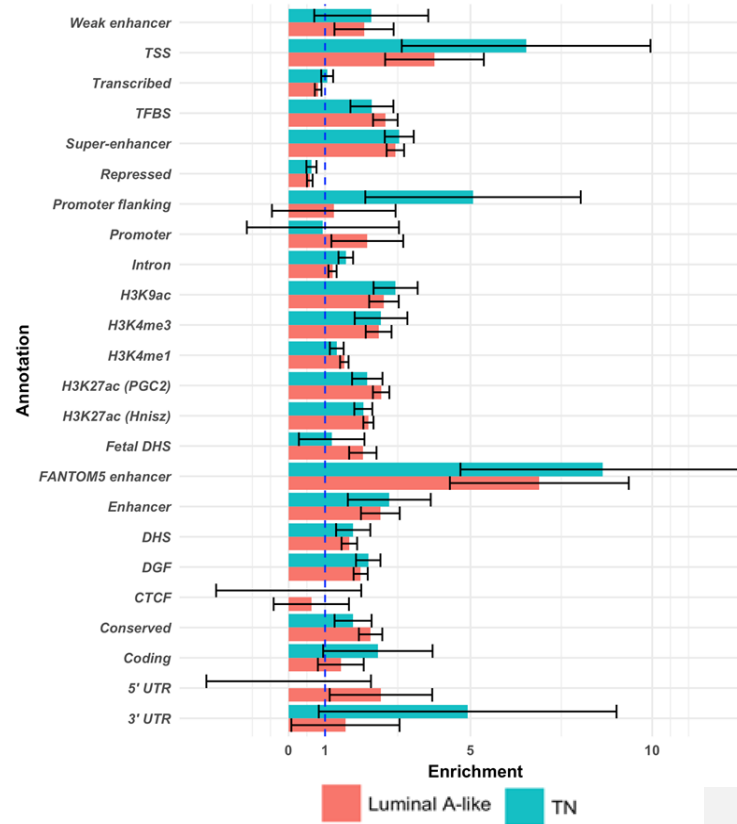
5. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2)

Supplementary figure 9. a) Enrichment analysis¹ results for 24 non-cell-type-specific, publicly available annotations for luminal A-like subtypes and triple-negative TN subtypes (*n* = 45,253 effective luminal A-like cases, *n* = 8,602 effective triple-negative cases, *n* = 91,477 controls). **b)** Enrichment analysis¹ results for 24 main annotations with ± 500 bp extension for luminal A-like subtypes and triple-negative TN subtypes. No significant differences were found between luminal A-like and triple-negative TN after adjusting for multiple testing.

a)



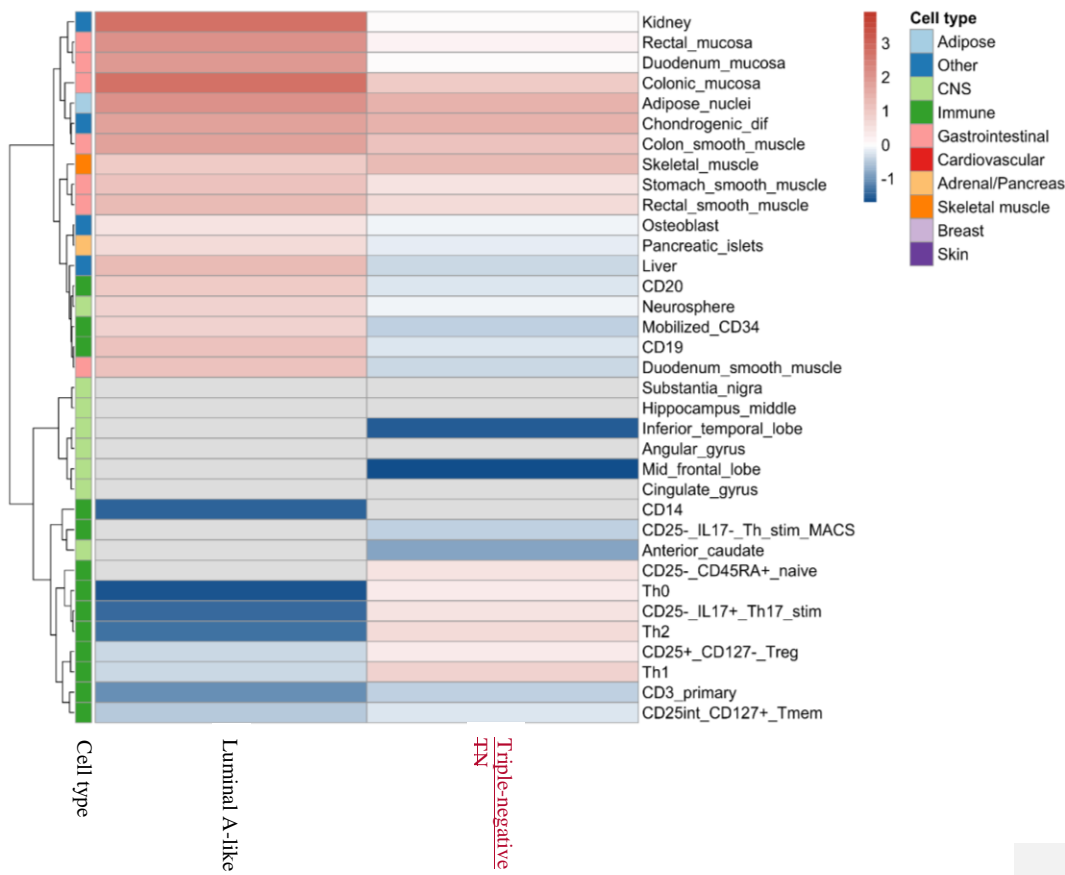
b)



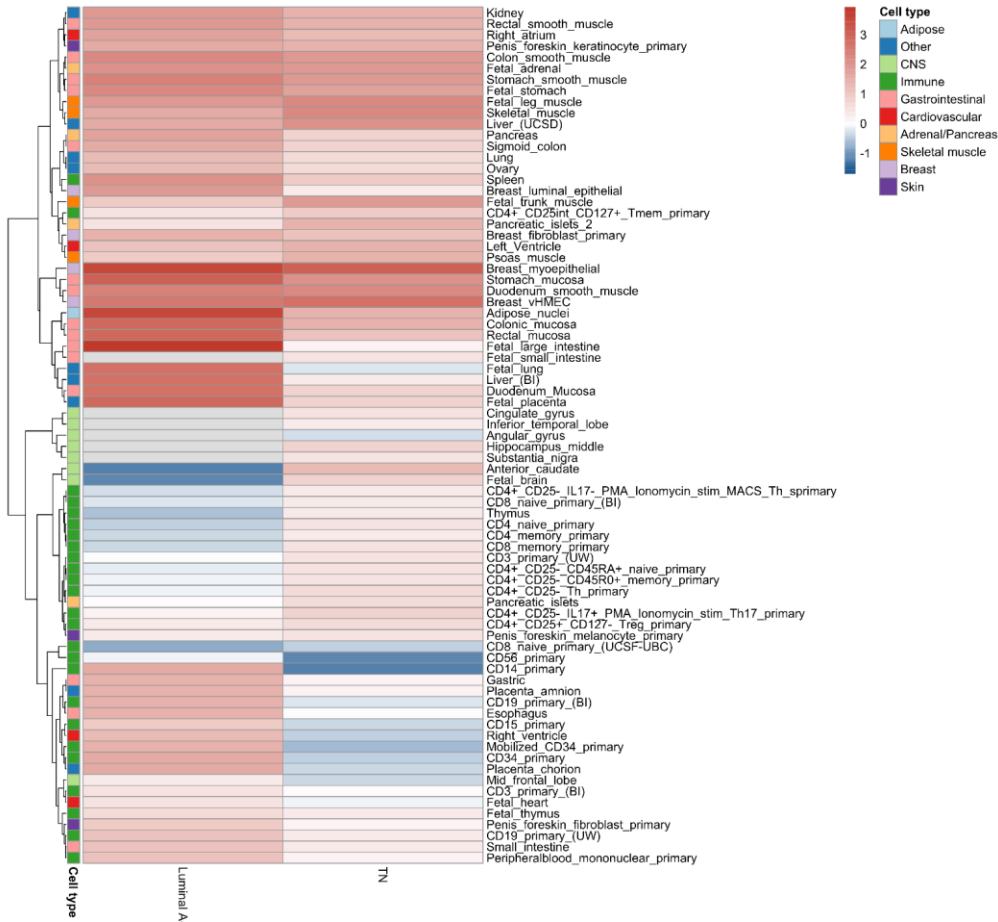
¹ Error bars represent Jackknife standard errors around the estimates of enrichment.

Supplementary figure 10. Enrichment analysis results for 220 cell-type-specific annotations of four histone marks - H3K4me1, H3K4me3, H3K9ac and H3K27ac – in the luminal A-like and triple-negative TN subtypes. Both luminal A-like and triple-negative TN subtypes were enriched for gastrointestinal cell types and suppression of central nervous system cells.

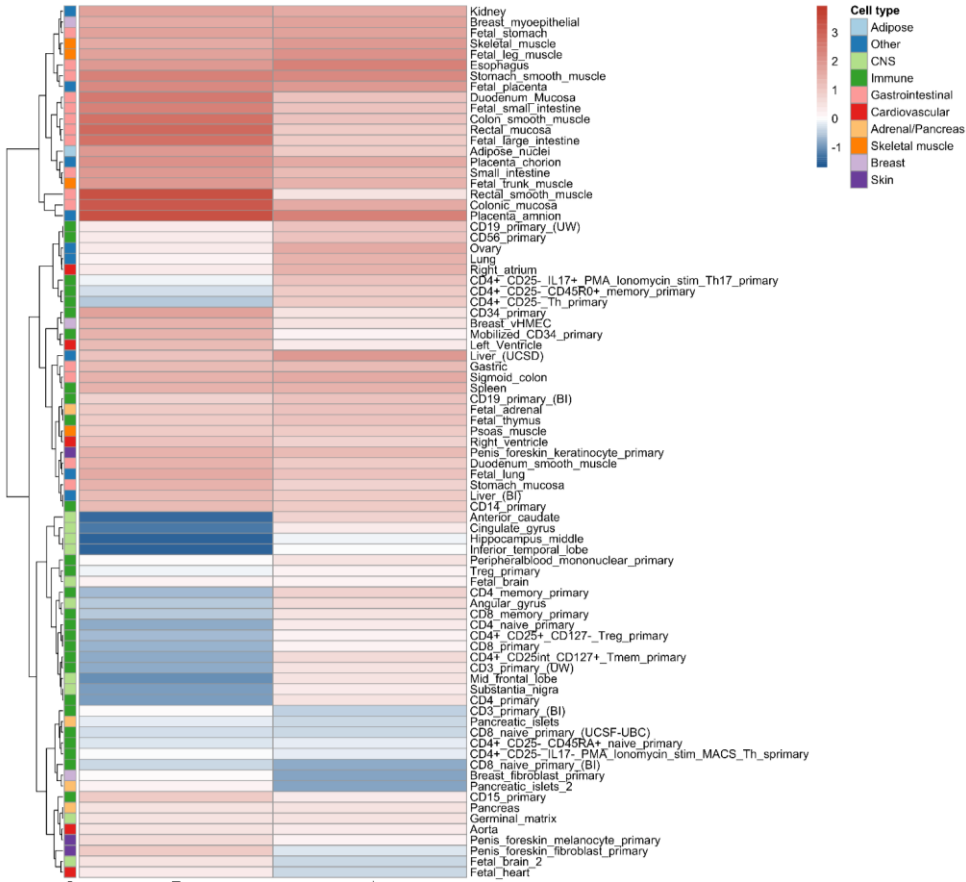
a) Heatmap showing patterns of cell-type specific enrichment for histone marks H3K27ac in luminal A-like tumors and TN tumors



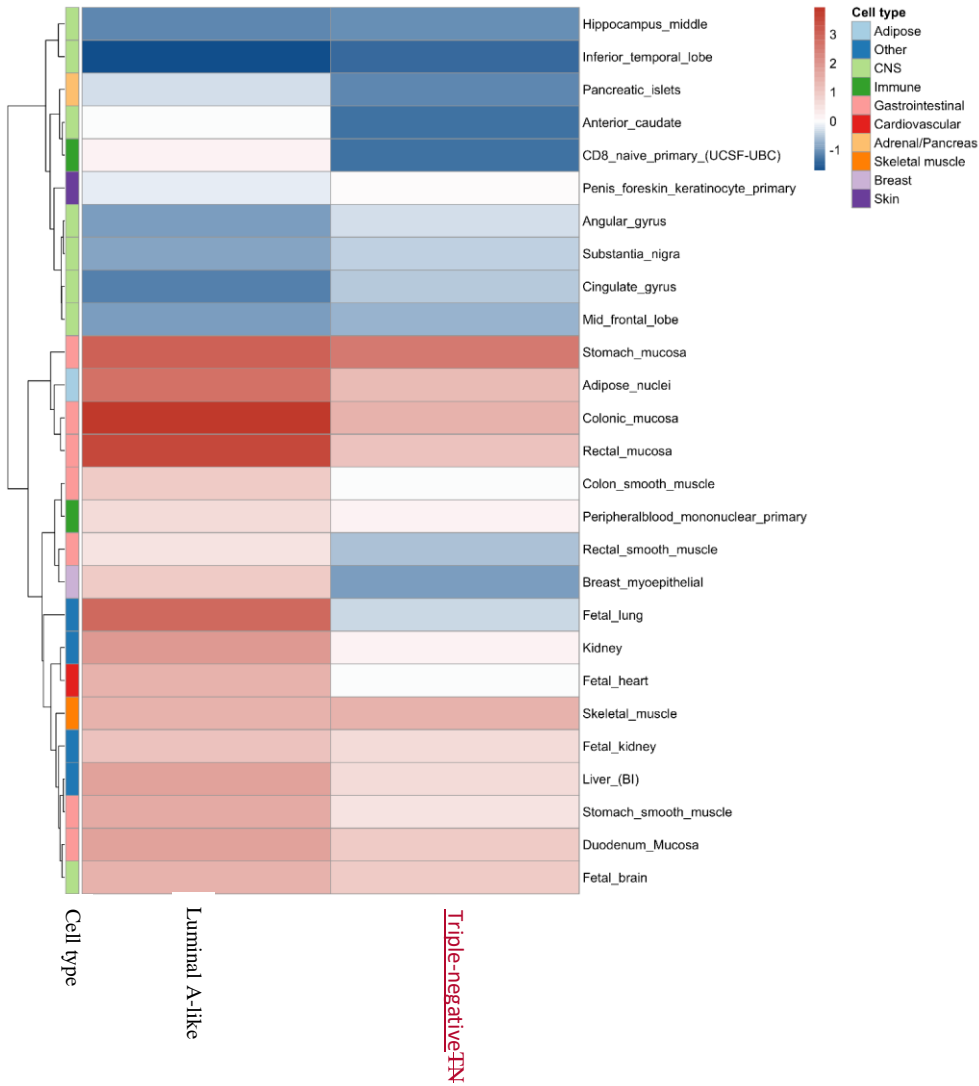
b) Heatmap showing patterns of cell-type specific enrichment for histone marks H3K4me1 in luminal A-like tumors and **triple-negative TN** tumors



c) Heatmap showing patterns of cell-type specific enrichment for histone marks H3K4me3 in luminal A-like tumors and **triple-negative TN** tumors



d) Heatmap showing patterns of cell-type specific enrichment for histone marks H3K9ac in luminal A-like tumors and triple-negative TN tumors



Supplementary Note

eQTL Analysis

Data from breast cancer tumors and adjacent normal breast tissue were accessed from The Cancer Genome Atlas (TCGA)¹. Germline variant genotypes (Affymetrix 6.0 arrays) were processed and imputed to the 1000 Genomes reference panel (October 2014) and European ancestry ascertained as previously described². Tumor tissue copy number was estimated from the Affymetrix 6.0 and called using the GISTIC2 algorithm³. 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 Consortium⁴. 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 described⁵. eQTL analyses were performed using the MatrixEQTL program in R⁶.

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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)⁷ in MCF7 cells, and genome-wide chromosome conformation capture (Hi-C) in HMECs⁸. We used breast cell line computational enhancer-promoter correlations (PreSTIGE⁹, IM-PET¹⁰, FANTOM5¹¹) breast cell super-enhancer¹², breast tissue-specific expression variants (eQTL) from multiple independent studies (TCGA (normal

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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 (ENCODE¹⁴). To assess the impact of intragenic variants, we evaluated their potential to alter primary protein coding sequence and splicing using Ensembl Variant Effect Predictor¹⁵ using MaxEntScan and dbcsSNV 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 variants) 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.

Global genomic enrichment analyses

We performed stratified LD score regression analyses¹⁶⁻¹⁸ as previously described² for two major intrinsic-like subtypes, luminal A-like and triple-negative, using the summary statistics from the meta-analyses of OncoArray, iCOGs, and CIMBA. The analysis included all variants in the 1000 Genome Project Phase 1v3 release with MAF $>1\%$ and imputation quality score $R^2 > 0.3$ in the OncoArray data. We restricted analysis to all variants 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 variants, 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)¹⁶. 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, variants 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 triple-negative 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 triple-negative 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 triple-negative subtypes we had no concern about a type one error.

Two-stage polytomous model

The two-stage polytomous logistic regression model allows us to efficiently test for genetic associations while accounting for tumor marker correlations and large amounts of missing tumor data¹⁹. We used this method to detect breast cancer susceptibility variants while taking account of four tumor characteristics: estrogen receptor (ER; ER-positive vs ER-negative), progesterone receptor (PR; PR-positive vs PR-negative), human epidermal growth factor receptor 2 (HER2; HER2-positive vs HER2-negative), and grade (defined as grade 1, grade 2, and grade 3). Below we describe in greater detail how we applied this method

In our study, we investigated for underlying heterogenous associations according to ER, PR, HER2, and grade; however, we will first start the discussion of fitting a two-stage polytomous model by first focusing on ER, PR, and HER2, and then discuss including grade in the model. The cross combination of ER, PR, and HER2 results in eight distinct breast cancer subtypes ($8 = 2 \times 2 \times 2$). Let N denote the total sample size and let D_i denote the disease status of i th subject which can take values from $\{0, 1, 2, \dots, 8\}$ and $i = 1, 2, \dots, N$. $D_i = 0$ represent a control, and $D_i = m$ represent the i th subject with the breast cancer subtypes M . Let G_i denote the genotype of a variant for i th subject, taking values from $\{0, 1, 2\}$. Let X_i denote the other covariates for the i th subject, for example principal components or age. In the first stage of the model, we fit a standard “saturated” polytomous logistic regression model:

$$\Pr(D_i = m | G_i, X_i) = \frac{\exp(\beta_m G_i + \boldsymbol{\eta}_m^T \mathbf{X}_i)}{1 + \sum_{m=1}^8 \exp(\beta_m G_i + \boldsymbol{\eta}_m^T \mathbf{X}_i)}, \quad (1)$$

where β_m is the regression coefficient for a variant (G) associated with the mth subtype and $\boldsymbol{\eta}_m$ is the vector of regression coefficients for the other covariate (X) associated with mth subtype.

Each cancer subtype m is defined through a unique combination of ER, PR, and HER2; therefore, we can alternatively index the parameters β_m as $\beta_{s_1 s_2 s_3}$, where $s_1, s_2, s_3 \in \{0, 1\}$ for the three binary tumor characteristics. Originally, β_1 represented the regression coefficient of the ER-, PR-, HER2- subtype. With this indexing, β_1 can be alternatively written as β_{000} and, thus with this reparameterization we can represent the log odds ratio of the eight subtypes as:

$$\beta_{s_1 s_2 s_3} = \theta^{(0)} + \theta_1^{(1)} s_1 + \theta_2^{(1)} s_2 + \theta_3^{(1)} s_3 + \theta_{12}^{(2)} s_1 s_2 + \theta_{13}^{(2)} s_1 s_3 + \theta_{23}^{(2)} s_2 s_3 + \theta_{123}^{(3)} s_1 s_2 s_3, \quad (2)$$

where $\theta_0^{(0)}$ represents the case-control log odds ratio for a reference subtypes versus the controls. We have chosen ER-, PR-, HER2- as the reference subtype, but any subtype can be chosen as the reference subtype. $\theta_k^{(1)}$ represents the case-case log odds ratio for the kth tumor characteristic after adjusting for the other tumor characteristics. We also refer $\theta_k^{(1)}$ as the main effect of the kth tumor characteristic. $\theta_{k_1 k_2}^{(2)}$ represents how the case-case log odds ratio associated with k_1 th tumor characteristic is modified by levels of the k_2 th tumor characteristic and vice versa. We also refer to $\theta_{k_1 k_2}^{(2)}$ as the pairwise interaction between the k_1 th tumor characteristic and the k_2 th tumor characteristic. $\theta_{123}^{(3)}$ represents the third order interaction of the three tumor characteristics. This decomposition is equivalent to the first stage polytomous logistic regression since both the first stage and second stage have eight parameters. We can specify different two stage models by assuming different second stage parameters to be equal to 0. For example, the baseline two-stage model is represented by:

$$\beta_{s_1 s_2 s_3} = \theta^{(0)}. \quad (3)$$

This baseline model assumes all of the subtypes have the same log odds ratio and is equivalent to a standard case-control logistic regression testing the association between an exposure and breast cancer, irrespective of tumor subtypes. We can also constrain all of the second stage pairwise interactions and higher order interactions to be 0:

$$\beta_{s_1 s_2 s_3} = \theta^{(0)} + \theta_1^{(1)} s_1 + \theta_2^{(1)} s_2 + \theta_3^{(1)} s_3. \quad (4)$$

This additive two-stage model assumes the case-case log odds ratio of a tumor characteristic are not affected by interactions with the other tumor characteristics.

By adding the second stage pairwise interactions parameters into the model, we can also construct the pairwise interaction two-stage polytomous model:

$$\beta_{s_1 s_2 s_3} = \theta^{(0)} + \theta_1^{(1)} s_1 + \theta_2^{(1)} s_2 + \theta_3^{(1)} s_3 + \theta_{12}^{(2)} s_1 s_2 + \theta_{13}^{(2)} s_1 s_3 + \theta_{23}^{(2)} s_2 s_3. \quad (5)$$

This model evaluates how two tumor characteristics are modified by each other. For example, $\theta_{12}^{(2)}$ measures how the case-case log odds ratio associated of ER is modified by the status of PR and vice versa. If we further add the three-way interaction term between ER, PR, and HER2, then this model becomes saturated (as shown in in Equation 2) and is equivalent to the polytomous logistic regression.

When we add the three-level ordinal variable tumor grade into the model, we can define 24 (2x2x2x3) breast cancer subtypes. We can apply the same decomposition as implemented with three tumor characteristics to provide the following additive two-stage model:

$$\beta_{s_1 s_2 s_3 s_4} = \theta^{(0)} + \theta_1^{(1)} s_1 + \theta_2^{(1)} s_2 + \theta_3^{(1)} s_3 + \theta_4^{(1)} s_4, \quad (6)$$

where $\theta_4^{(1)}$ is the main effect of grade and s_4 can take the values from {1, 2, 3}. In this model, we assume the grade main effect linearly changes, meaning the average log odds ratios difference between grade 3 versus grade2 is the same the as the difference between grade 2 versus grade1.

We can always describe the link between the first stage parameters and second stage parameters in Equation (6) in matrix form:

$$\begin{array}{l}
\text{ER} - \text{PR} - \text{HER2} - \text{grade1} \\
\text{ER} + \text{PR} - \text{HER2} - \text{grade1} \\
\text{ER} - \text{PR} + \text{HER2} - \text{grade1} \\
\text{ER} + \text{PR} + \text{HER2} - \text{grade1} \\
\text{ER} - \text{PR} - \text{HER2} + \text{grade1} \\
\text{ER} + \text{PR} - \text{HER2} + \text{grade1} \\
\text{ER} - \text{PR} + \text{HER2} + \text{grade1} \\
\text{ER} + \text{PR} + \text{HER2} + \text{grade1} \\
\dots \\
\text{ER} + \text{PR} + \text{HER2} + \text{grade3}
\end{array}
\boldsymbol{\beta} = \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \\ \beta_5 \\ \beta_6 \\ \beta_7 \\ \beta_8 \\ \dots \\ \beta_{24} \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & 0 & 1 \\ 1 & 1 & 0 & 0 & 1 \\ 1 & 0 & 1 & 0 & 1 \\ 1 & 1 & 1 & 0 & 1 \\ 1 & 0 & 0 & 1 & 1 \\ 1 & 1 & 0 & 1 & 1 \\ 1 & 0 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 & 1 \\ \dots & \dots & \dots & \dots & \dots \\ 1 & 1 & 1 & 1 & 3 \end{bmatrix} \begin{bmatrix} \theta^{(0)} \\ \theta_1^{(1)} \\ \theta_2^{(1)} \\ \theta_3^{(1)} \\ \theta_4^{(1)} \end{bmatrix} = \mathbf{Z} \begin{bmatrix} \theta^{(0)} \\ \boldsymbol{\theta}^H \end{bmatrix} = \mathbf{Z}\boldsymbol{\theta}, \quad (7)$$

where $\boldsymbol{\beta}$ is a vector of regression coefficients of the first stage parameters, $\boldsymbol{\theta}$ is the vector of all the second stage parameters, and $\boldsymbol{\theta}^H$ is a vector of second stage main effects.

Hypothesis testing of two-stage polytomous logistic regression

Under the two-stage model framework, there are three different tests we can construct. The first is the global association test:

$$H_0: \theta^{(0)} = 0 \text{ and } \boldsymbol{\theta}^H = \mathbf{0} \text{ versus } H_1: \text{either } \theta^{(0)} \neq 0 \text{ or } \boldsymbol{\theta}^H \neq \mathbf{0}. \quad (8)$$

This test is designed to test whether a variant is associated with any of the 24 breast cancer subtypes. If the null hypothesis is rejected under this setting, then at least one of the first stage subtype case-control log odds ratios β_m is significantly not equal to 0. The second test is the global heterogeneity test:

$$H_0: \boldsymbol{\theta}^H = \mathbf{0} \text{ versus } H_1: \boldsymbol{\theta}^H \neq \mathbf{0}. \quad (8)$$

This test is designed to test whether the associations between a variant and any two breast cancer subtypes are significantly different from each other. If the null hypothesis is rejected under this setting, then we can conclude that at least two of the first stage subtypes case-control log odds ratios are significantly different with each other ($\beta_{m_1} \neq \beta_{m_2}$).

If the global heterogeneity test is significant, then we can construct the third hypothesis tests, the specific tumor marker heterogeneity test:

$$H_0: \boldsymbol{\theta}_{(k)}^H = 0 \text{ versus } H_1: \boldsymbol{\theta}_{(k)}^H \neq 0. \quad (9)$$

This test is designed to test which tumor character is the source of the observed heterogeneity in the global heterogeneity test. Under the additive two-stage model in Equation (6), for example, we can test $H_0: \theta_1^{(1)} = 0$ versus $H_1: \theta_1^{(1)} \neq 0$. This is designed to test whether the case-case log odds ratio of ER is significant not equaling to 0 after adjusting for the effects of PR, HER2 and grade.

Mixed effect two-stage polytomous model

Although the additive two-stage model decreases the degrees of freedoms compared to the first stage polytomous logistic regression, the degrees of freedom of the two-stage model are still penalized when additional tumor characteristics are included into the model. To address this issue, we developed the mixed effect two-stage polytomous model to enter tumor characteristic variables into the model as either fixed- or random-effect terms. In this model, we keep the second stage main effect of ER ($\theta_1^{(1)}$) as a fixed effect since there is strong *a priori* evidence that ER is a common source of heterogeneity²⁰. On the other hand, as there is minimal evidence suggesting that tumor characteristics such as PR, HER2, and grade are sources of heterogeneity, we assume the case-case parameter of PR ($\theta_2^{(1)}$), HER2 ($\theta_3^{(1)}$) and grade ($\theta_4^{(1)}$) as random effects. These random parameters have an assumed arbitrary distribution with mean 0 and variance σ^2 . We always keep the baseline effect $\theta^{(0)}$ as fixed since it captures the overall association between a variant and breast cancer. Under the mixed effect two stage model, the global test for association is:

$$H_0: \theta^{(0)} = 0, \theta_1^{(1)} = 0, \sigma^2 = 0 \text{ versus } H_1: \text{either } \theta^{(0)}, \theta_1^{(1)}, \text{ or } \sigma^2 \neq 0 \quad (10)$$

The rejection of the null hypothesis implies that the variant is significantly associated with at least one of the 24 breast cancer subtypes. The global heterogeneity test under the mixed effect two-stage model would be:

$$H_0: \theta_1^{(1)} = 0 \text{ and } \sigma^2 = 0 \text{ versus } H_1: \text{either } \theta_1^{(1)} \text{ or } \sigma^2 \neq 0. \quad (11)$$

The rejection of the null hypothesis would imply that the variant's associations between at least two breast cancer subtypes are significantly different. However, the specific tumor marker heterogeneity test for a specific tumor marker is not applied in the mixed effect two-stage model because it requires the estimate of case-case log odds ratio of PR, HER2 and grade which are not estimated when modeled as random effects.

Two-stage model for intrinsic subtypes of breast cancer

In previous sections, we showed how the first stage case control log odds ratios of breast cancer subtypes are decomposed to the case control log odds ratio of a reference subtype and the into case-case parameters of tumor characteristics. Using the hierarchical second stage decomposition, the two-stage model can also estimate the case control log odds ratio of specific breast cancer subtypes of interest. In our study we defined five intrinsic-like breast cancer subtypes based on tumor status of ER, PR, HER2 and grade: (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) triple-negative (TN; ER-, PR-, HER2-). To estimate the case-control log odds ratios of these five intrinsic subtypes we can construct the two-stage model as:

$$\begin{array}{l}
\text{ER - PR - HER2 - grade1} \\
\text{ER + PR - HER2 - grade1} \\
\text{ER - PR + HER2 - grade1} \\
\text{ER + PR + HER2 - grade1} \\
\text{ER - PR - HER2 + grade1} \\
\text{ER + PR - HER2 + grade1} \\
\text{ER - PR + HER2 + grade1} \\
\text{ER + PR + HER2 + grade1} \\
\text{...} \\
\text{ER + PR + HER2 + grade3}
\end{array}
\boldsymbol{\beta} = \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \\ \beta_5 \\ \beta_6 \\ \beta_7 \\ \beta_8 \\ \dots \\ \beta_{24} \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots \\ 0 & 1 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} \theta_1 \\ \theta_2 \\ \theta_3 \\ \theta_4 \\ \theta_5 \end{bmatrix} \quad \begin{array}{l} \text{Luminal A - like, low grade} \\ \text{Luminal B - like} \\ \text{Luminal B/HER2 - negative - like} \\ \text{HER2 enriched - like} \\ \text{Triple - negative} \end{array} \quad (12)$$

Under this model, the second stage parameters provide estimates of case-control log odds ratios for the five tumor subtypes. This model is similar to directly fitting a polytomous logistic regression.

However, we have incorporated into the two-stage model an efficient missing data algorithm that allows to take advantage of subjects with incomplete tumor characteristic data. The missing data algorithm has been described in detail elsewhere [1].

Modified LD score regression

Since the two-stage polytomous logistic regression implements an EM algorithm to account for missing tumor characteristics data, the effective sample size is not equivalent to the sample size of cases with complete tumor characteristic data. In this case the sample size is not available, but the log odds ratio for each variant $\hat{\beta}_j$ and the standard error s_j are given.

Under a case-control study, we consider the logistic regression model

$$\log \left(\frac{p}{1-p} \right) = \alpha + (\boldsymbol{\beta}^{(j)})^T \mathbf{X},$$

where $\boldsymbol{\beta}^{(j)} = (\beta_1^{(j)}, \beta_2^{(j)}, \dots, \beta_M^{(j)})$ are the joint effect sizes. We define the heritability as $h^2 = \text{var}((\boldsymbol{\beta}^{(j)})^T \mathbf{X})$, assuming \mathbf{X} is standardized with mean 0 variance 1. If \mathbf{X} is in the original 0, 1, 2 scale, we multiply the $\hat{\beta}_j$ and s_j by $\sqrt{2p_j(1-p_j)}$ to standardize, where p_j is the minor allele frequency for the j th variant. Therefore, the expected chi-square statistics (z_j^2) of variant j is

$$\begin{aligned}
E(z_j^2 | l_j) &= \frac{E(\hat{\beta}_j^2 | l_j)}{s_j^2} = \frac{[E\{(\hat{\beta}_j - \beta_j)^2 | l_j\} + 2E[(\hat{\beta}_j - \beta_j)\beta_j | l_j] + E(\beta_j^2 | l_j)]}{s_j^2} \\
&= \frac{[E\{(\hat{\beta}_j - \beta_j)^2 | l_j\} + E(\beta_j^2 | l_j)]}{s_j^2} \\
&= 1 + \frac{E\{(\sum_k r_{jk} \beta_k^{(j)})^2\}}{s_j^2} \\
&= 1 + \frac{h^2 l_j}{M s_j^2},
\end{aligned} \tag{13}$$

where $l_j = \sum_k r_{jk}^2$ is the LD score of the variant j and $1/s_j^2$ is the effective sample size for variant j . The modified LD score regression formula is:

$$E(z_j^2 | l_j) = 1 + \frac{h^2 l_j}{M s_j^2}. \tag{14}$$

To estimate the genetic correlation between two traits, the expected value of $z_{1j}z_{2j}$ for a variant j is

$$\begin{aligned}
E(z_{1j}z_{2j} | l_j) &= \frac{E(\hat{\beta}_{1j} \hat{\beta}_{2j} | l_j)}{s_{1j}s_{2j}} \\
&= \frac{[E\{(\hat{\beta}_{1j} - \beta_{1j})(\hat{\beta}_{2j} - \beta_{2j}) | l_j\} + E(\beta_{1j}\beta_{2j} | l_j)]}{s_{1j}s_{2j}} \\
&= \frac{s_{12j}}{s_{1j}s_{2j}} + \frac{E(\sum_k r_{jk} \beta_{1k}^{(j)} \sum_k r_{jk} \beta_{2k}^{(j)} | l_j)}{s_{1j}s_{2j}} \\
&= \frac{s_{12j}}{s_{1j}s_{2j}} + \frac{\rho_g l_j}{M s_{1j}s_{2j}},
\end{aligned} \tag{15}$$

where ρ_g is the genetic covariance between the two different traits. Under this case, $1/s_{1j}^2$ and $1/s_{2j}^2$ are the effective sample size for variant j for the two traits respectively. The modified LD score regression for genetic covariance is

$$E(z_{1j}z_{2j} | l_j) = \frac{s_{12j}}{s_{1j}s_{2j}} + \frac{\rho_g l_j}{M s_{1j}s_{2j}}. \tag{16}$$

The genetic correlation is given by $\frac{\rho_g}{\sqrt{h_1^2 h_2^2}}$.

Effective sample size of cases of two-stage polytomous model

The two-stage polytomous model implements the EM algorithm to impute missing tumor characteristics; therefore, the effective sample size of cases is not equivalent to the actual number of cases with available tumor characteristic data. We estimated the effective sample sizes to help demonstrate the benefit of using the EM algorithm to impute missing tumor characteristics and to aid comparability with previous studies (**Supplementary Table 4**). To estimate the effective sample size, suppose we have a complete dataset with no missing tumor characteristics, the sample size is n_k for the k th subtype and n_0 for the control. If we fit a two-stage polytomous model for the j th variant, the corresponding log odds ratio for k th subtype is $\hat{\beta}_{jk}$ and the standard error is s_{jk} . Then, approximately:

$$\text{var}(\hat{\beta}_{jk}|p_j) \approx \frac{n_0 + n_k}{2 * p_j(1 - p_j)(n_0 n_k)},$$

where p_j is the MAF of the j th variant. Now we consider fitting a two-stage polytomous model with missing tumor characteristics. Given the standard error s_{jk} of the log odds ratio and the control sample size, we have the estimate of effective number of cases as,

$$\hat{n}_k = \left(\frac{1}{n_0} - 2s_{jk}^2 p_j(1 - p_j) \right)^{-1}.$$

We used the median estimates of effective sample size of cases for all variants as the final estimate.

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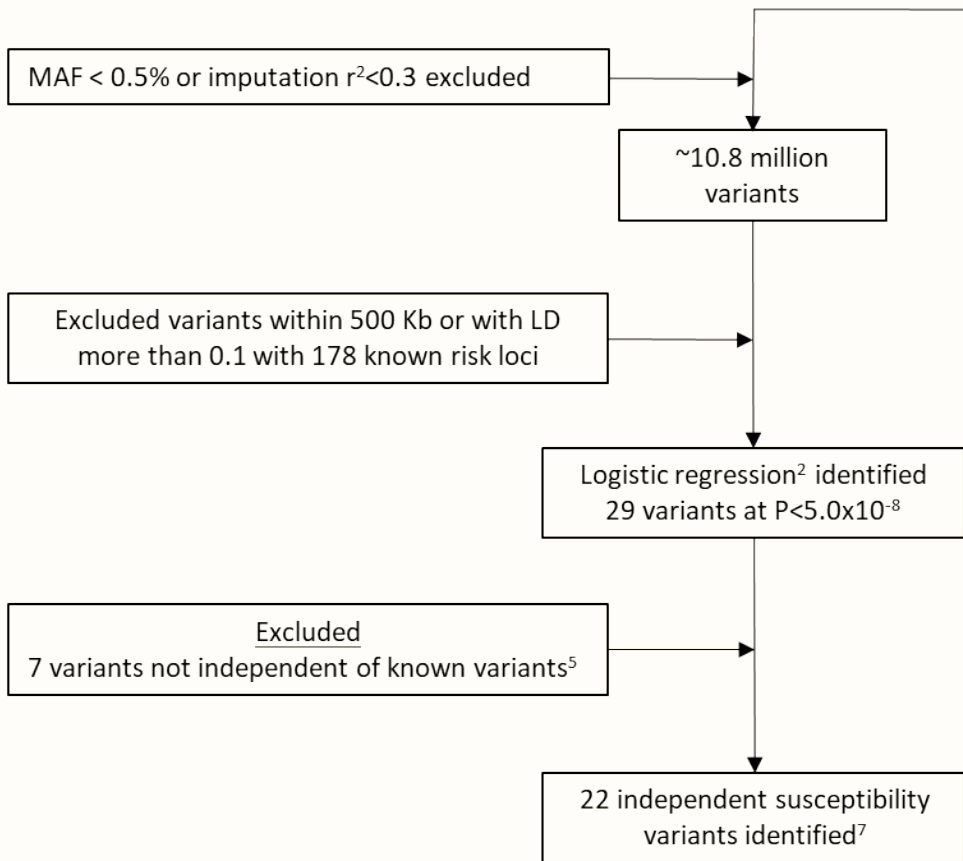
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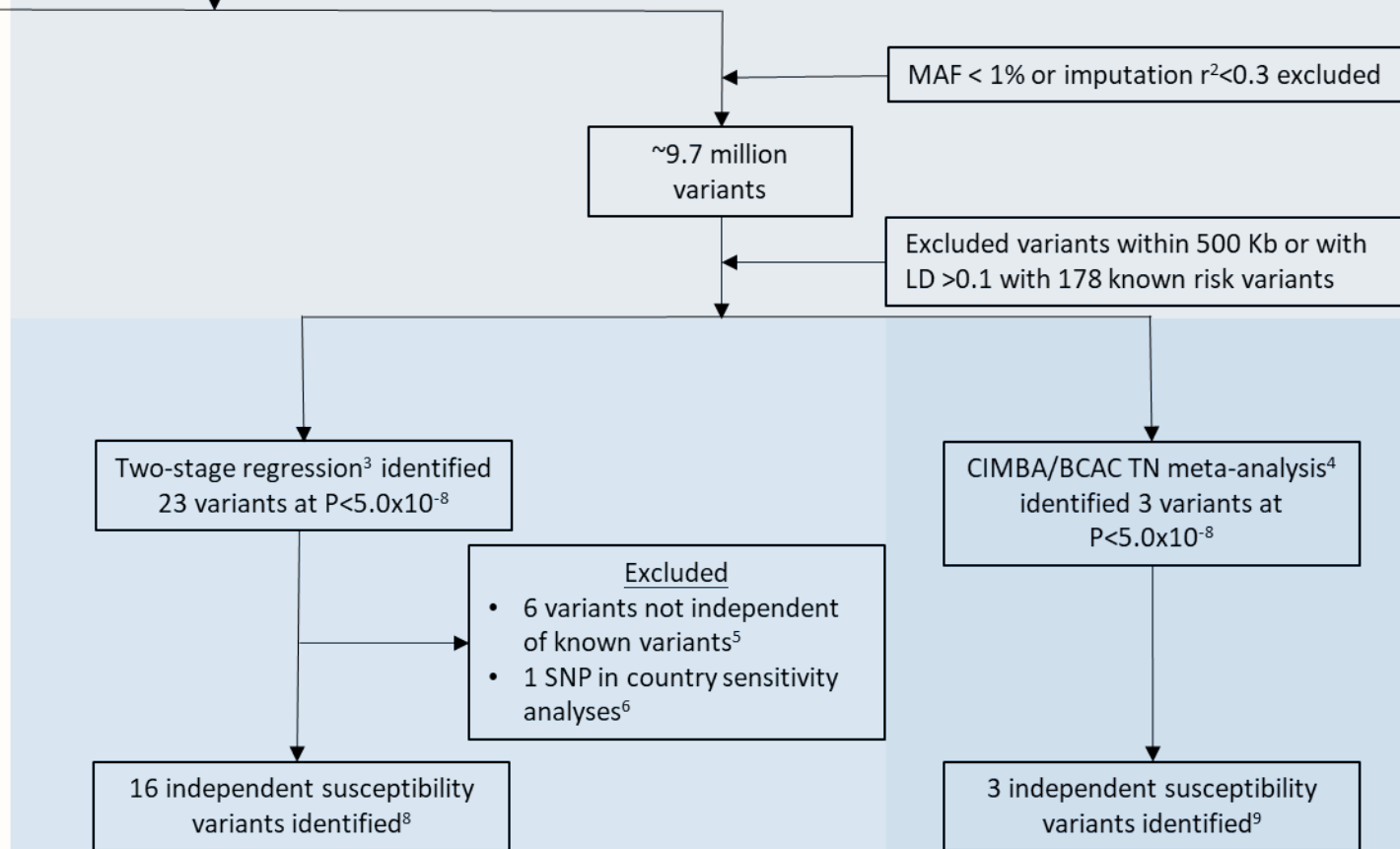
Etienne, France); Sandra Fert Ferrer (Hôtel Dieu Centre Hospitalier, Chambéry, France); Véronique Mari (Centre Antoine Lacassagne, Nice, France); Laurence Vénat-Bouvet (CHU Limoges, France); Capucine Delnatte, Stéphane Bézieau (CHU Nantes, France); Isabelle Mortemousque (CHU Bretonneau, Tours and Centre Hospitalier de Bourges France); Florence Coulet, Chrystelle Colas, Florent Soubrier, Mathilde Warcoin (Groupe Hospitalier PitiéSalpêtrière, Paris, France); Johanna Sokolowska, Myriam Bronner (CHU Vandoeuvreles-Nancy, France); Marie-Agnès Collonge-Rame, Alexandre Damette (CHU Besançon, France); Paul Gesta (CHU Poitiers, Centre Hospitalier d'Angoulême and Centre Hospitalier de Niort, France); Hakima Lallaoui (Centre Hospitalier de La Rochelle); Jean Chiesa (CHU Nîmes Carémeau, France); Denise Molina-Gomes (CHI Poissy, France); Olivier Ingster (CHU Angers, France).

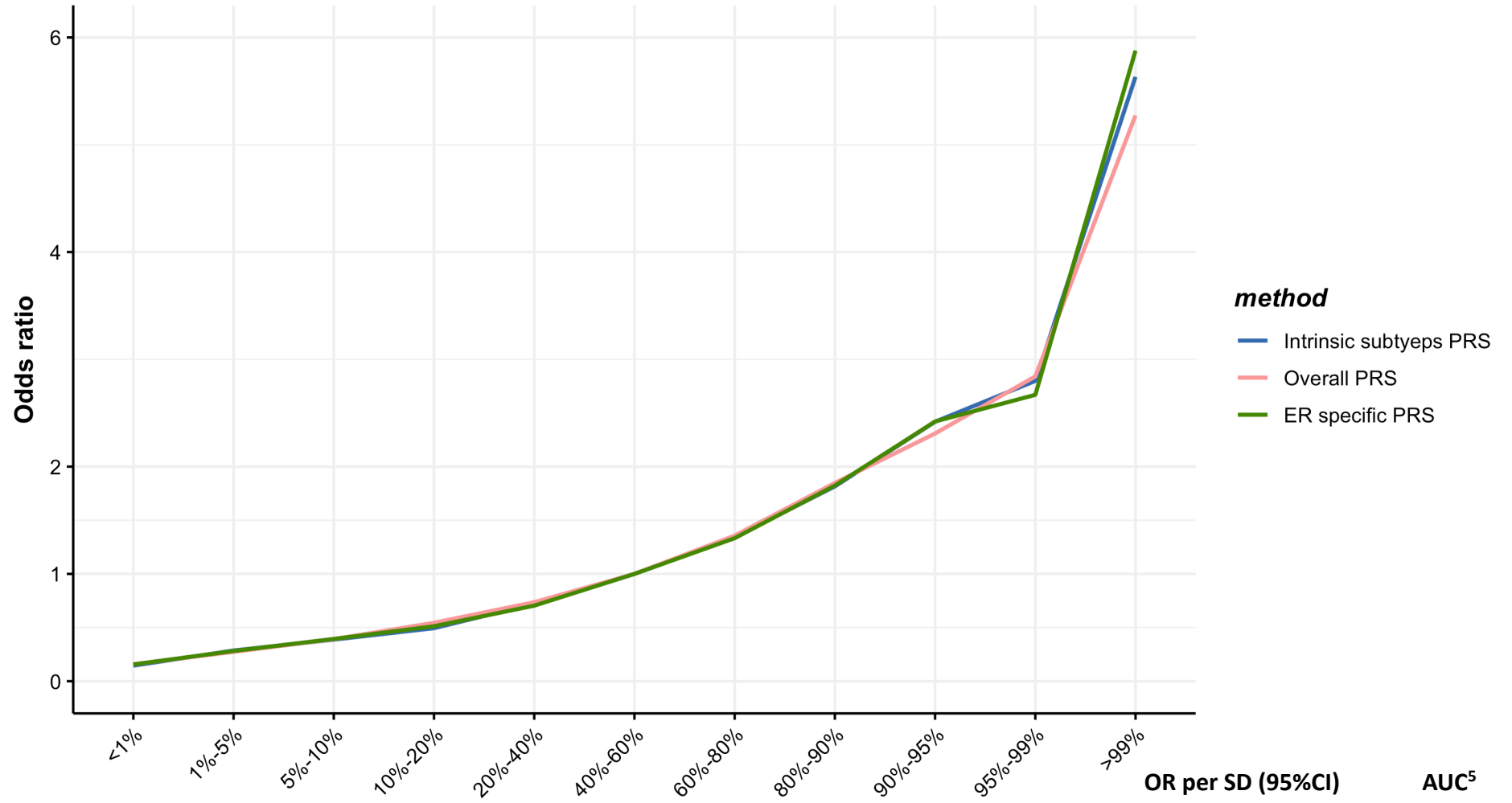
21 million Variants¹

Overall Breast Cancer Analyses



Analyses Accounting for Tumor Marker Heterogeneity





	<1%	1%-5%	5%-10%	10%-20%	20%-40%	40%-60%	60%-80%	80%-90%	90%-95%	95%-99%	>99%	OR per SD (95%CI)	AUC ⁵
Intrinsic subtypes PRS ORs¹	0.14	0.29	0.39	0.49	0.72	1.00	1.34	1.82	2.42	2.80	5.63	1.83 (1.78-1.88)	66.09
Overall PRS ORs²	0.16	0.27	0.39	0.54	0.74	1.00	1.36	1.85	2.31	2.84	5.27	1.80 (1.75-1.86)	65.73
ER Specific PRS ORs³	0.16	0.28	0.39	0.51	0.70	1.00	1.33	1.82	2.42	2.67	5.88	1.82 (1.77-1.87)	65.95

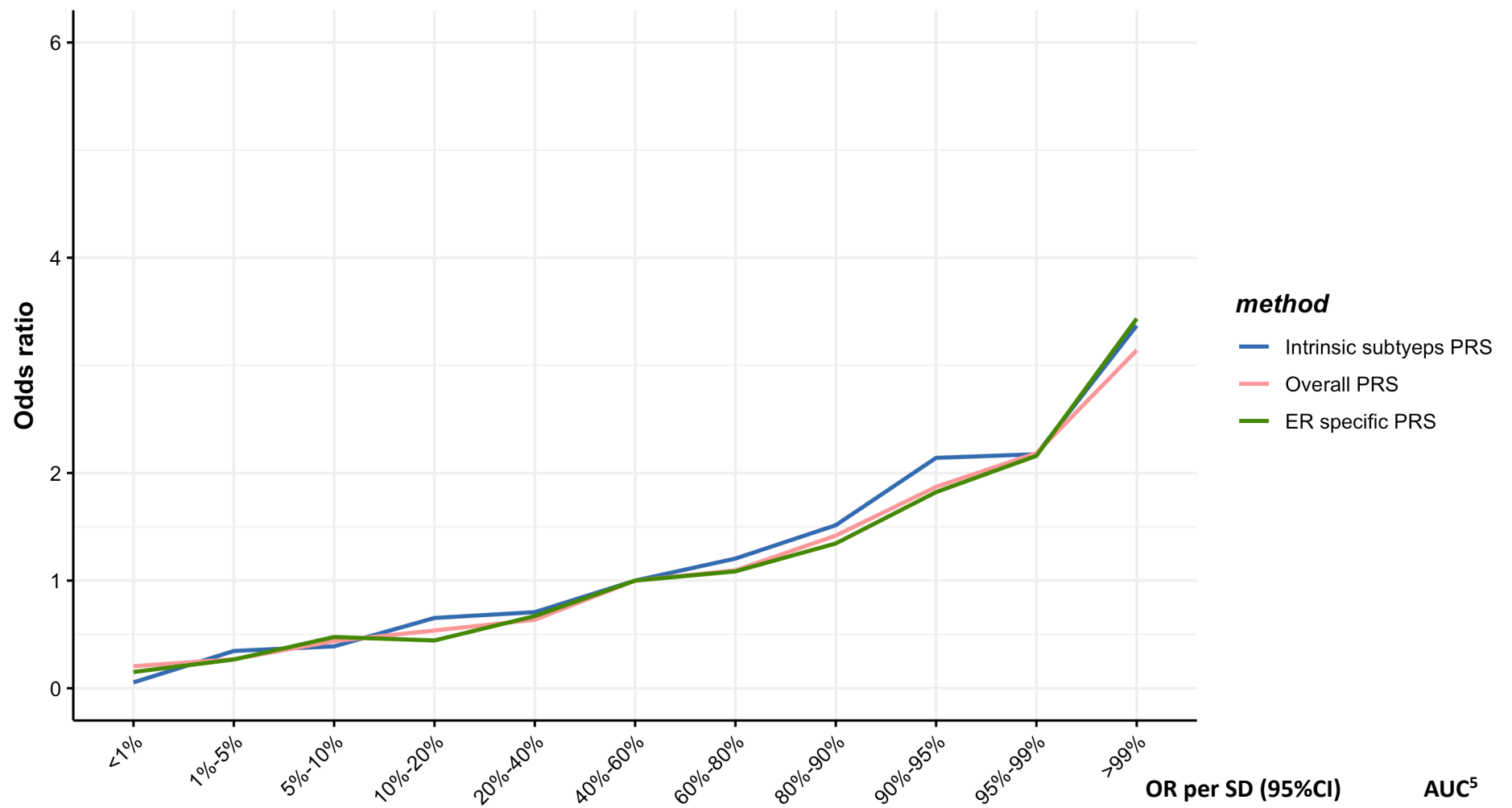
¹ Intrinsic-like subtypes PRS based on 330 SNPs (**Online Methods, Supplementary Table 19**)

² Overall breast cancer PRS with 313 SNPs previously reported²²

³ ER-specific PRS with 313 SNPs previously reported²²

⁴ Luminal A-like (ER+ and/or PR+, HER2-, grade 1 & 2).

⁵ Area under the curve



	<1%	1%-5%	5%-10%	10%-20%	20%-40%	40%-60%	60%-80%	80%-90%	90%-95%	95%-99%	>99%	OR per SD (95%CI)	AUC ⁵
Intrinsic subtypes PRS ORs¹	0.05	0.35	0.39	0.65	0.71	1.00	1.20	1.51	2.14	2.17	3.37	1.62 (1.54-1.70)	63.30
Overall PRS ORs²	0.20	0.27	0.44	0.54	0.64	1.00	1.10	1.42	1.87	2.19	3.14	1.62 (1.55-1.71)	63.36
ER Specific PRS ORs³	0.15	0.27	0.48	0.44	0.67	1.00	1.09	1.35	1.82	2.16	3.43	1.62 (1.54-1.70)	63.23

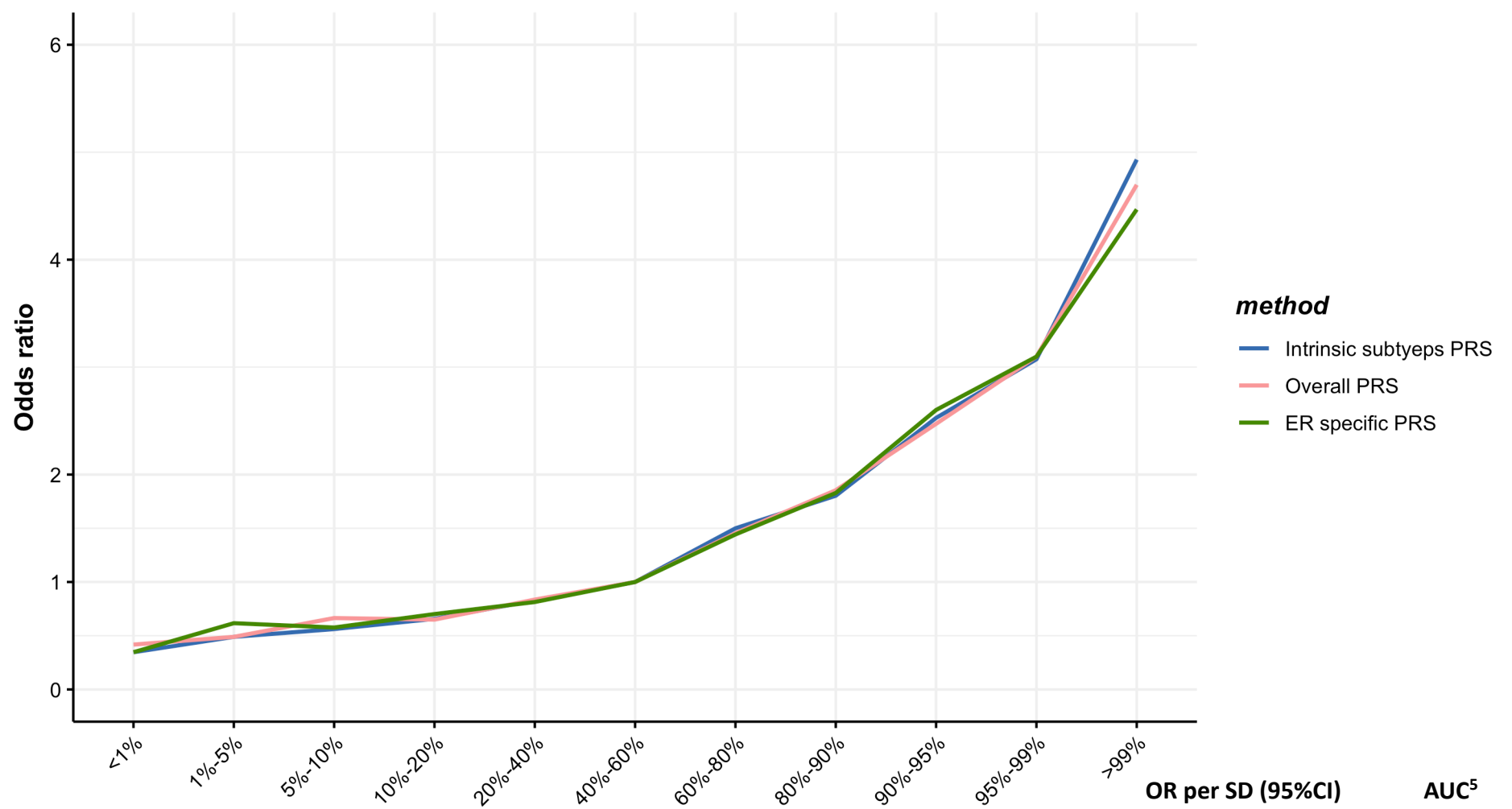
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⁴ Luminal A-like (ER+ and/or PR+, HER2-, grade 1 & 2).

⁵ Area under the curve



	OR per SD (95%CI)											AUC ⁵	
Intrinsic subtypes PRS ORs¹	0.35	0.49	0.56	0.66	0.83	1.00	1.50	1.80	2.53	3.07	4.93	1.69 (1.61-1.78)	64.31
Overall PRS ORs²	0.42	0.49	0.66	0.65	0.84	1.00	1.45	1.85	2.47	3.10	4.70	1.68 (1.60-1.77)	64.32
ER Specific PRS ORs³	0.35	0.62	0.58	0.70	0.81	1.00	1.44	1.83	2.60	3.10	4.47	1.66 (1.58-1.75)	64.00

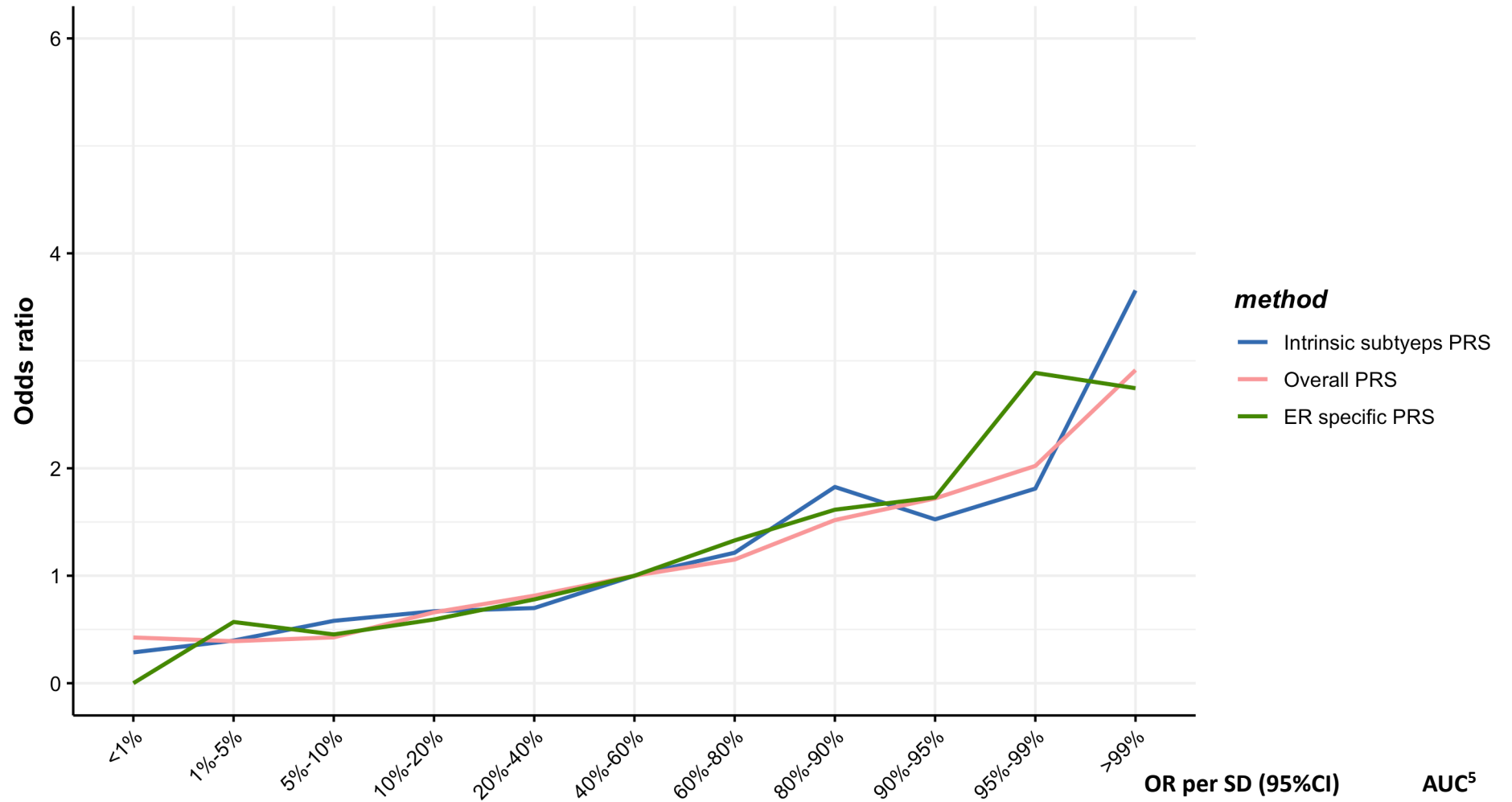
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⁴ Luminal A-like (ER+ and/or PR+, HER2-, grade 1 & 2).

⁵ Area under the curve



	<1%	1%-5%	5%-10%	10%-20%	20%-40%	40%-60%	60%-80%	80%-90%	90%-95%	95%-99%	>99%	OR per SD (95%CI)	AUC ⁵
Intrinsic subtypes PRS ORs¹	0.29	0.40	0.58	0.67	0.70	1.00	1.21	1.83	1.52	1.81	3.65	1.53 (1.42-1.65)	62.08
Overall PRS ORs²	0.43	0.39	0.43	0.66	0.81	1.00	1.15	1.52	1.72	2.02	2.91	1.49 (1.38-1.60)	60.93
ER Specific PRS ORs³	0.00	0.57	0.45	0.59	0.78	1.00	1.33	1.61	1.73	2.89	2.74	1.59 (1.48-1.71)	62.91

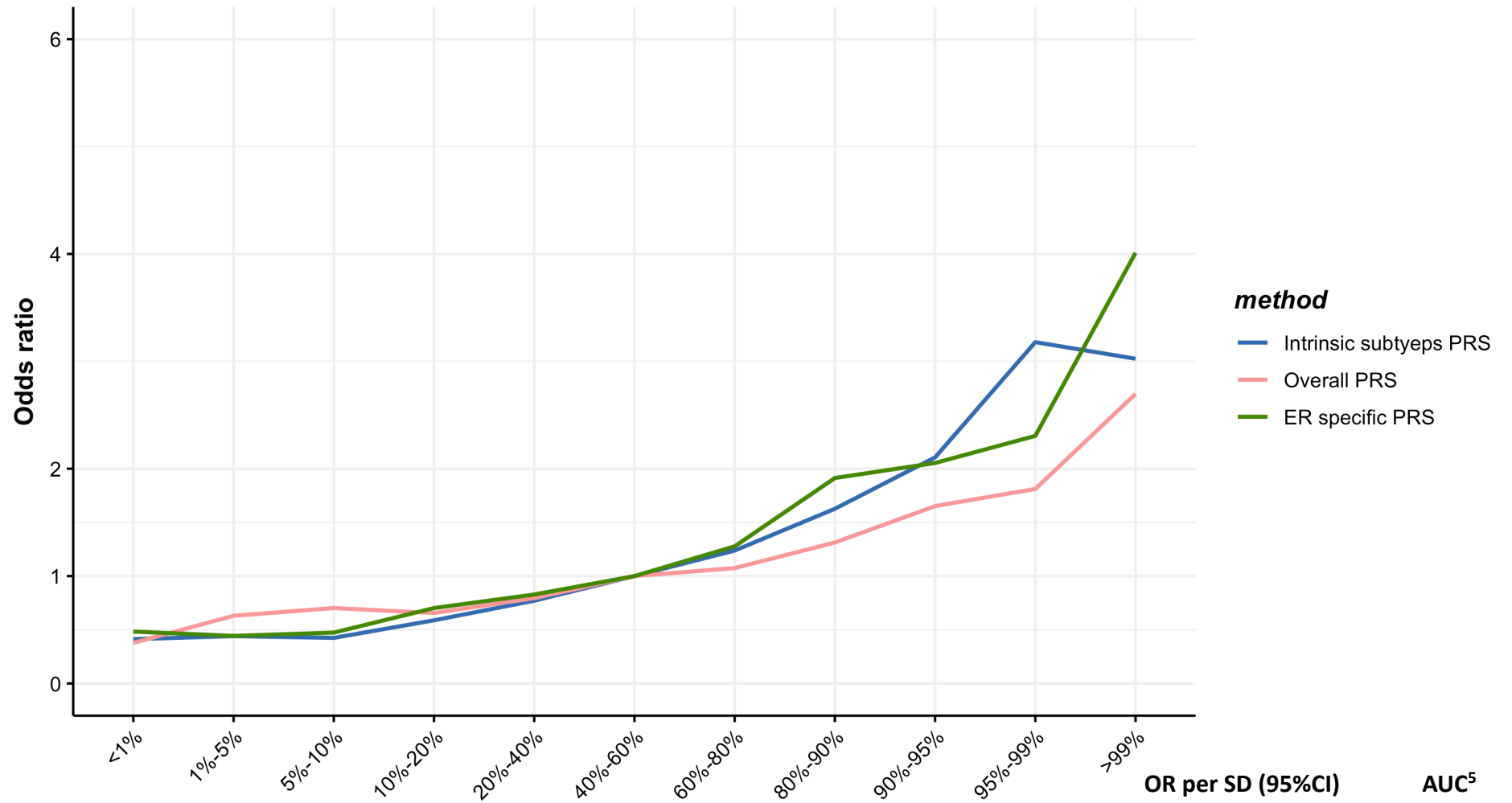
¹ Intrinsic-like subtypes PRS based on 330 SNPs (**Online Methods, Supplementary Table 19**)

² Overall breast cancer PRS with 313 SNPs previously reported²²

³ ER-specific PRS with 313 SNPs previously reported²²

⁴ Luminal A-like (ER+ and/or PR+, HER2-, grade 1 & 2).

⁵ Area under the curve



	OR per SD (95%CI)											AUC ⁵	
Intrinsic subtypes PRS ORs¹	0.41	0.44	0.42	0.59	0.77	1.00	1.24	1.63	2.11	3.18	3.02	1.65 (1.57-1.73)	63.58
Overall PRS ORs²	0.38	0.63	0.70	0.66	0.80	1.00	1.07	1.31	1.65	1.81	2.70	1.38 (1.31-1.44)	58.77
ER Specific PRS ORs³	0.48	0.44	0.47	0.70	0.83	1.00	1.28	1.91	2.05	2.31	4.01	1.59 (1.51-1.66)	62.76

¹ Intrinsic-like subtypes PRS based on 330 SNPs (**Online Methods, Supplementary Table 19**)

² Overall breast cancer PRS with 313 SNPs previously reported²²

³ ER-specific PRS with 313 SNPs previously reported²²

⁴ Luminal A-like (ER+ and/or PR+, HER2-, grade 1 & 2).

⁵ Area under the curve

Supplementary Table 1: BCAC studies contributing data¹, by genotyping initiative

Acronym	Study Name	Country	Study design	ICOGS				OncoArray				Other GWAS	
				Controls	Invasive	In Situ	Unknown Invasiveness	Controls	Invasive	In Situ	Unknown Invasiveness	Controls	Cases
ZSISTER	The Two Sister Study	USA	Case-only study					919	151	1			
ABCFS	Australian Breast Cancer Family Study	Australia	Case-control study	551	322			187	1117			285	282
ABCS	Amsterdam Breast Cancer Study	Netherlands	Case-control study	1628	771			189	347				
ABC5-F	Amsterdam Breast Cancer Study – Familial	Netherlands	Case-only study		1002	106							
ABC7B	Australian Breast Cancer Tissue Bank	Australia	Case-control study					375	947	6			
AHS	Agricultural Health Study	USA	Prospective cohorts: nested case-control studies					1137	513	1			
BBCC	Bavarian Breast Cancer Cases and Controls	Germany	Case-control study	453	438	8		253	403	8			
BBCS	British Breast Cancer Study	UK	Case-control study	1396	1404	106	2	442	122			1224	1609
BCES	Breast Cancer Employment and Environment Study	Australia	Case-control study					835	783				
BCFR	Breast Cancer Family Registry	USA, Canada, Australia	Case-control study									2251	3129
BCFR-NY	New York site of the Breast Cancer Family Registry	USA	Case-control study					27	401	53			
BCFR-PA	Philadelphia site of the Breast Cancer Family Registry	USA	Case-control study					63	6	70			
BCFR-UTAH	Utah site of the Breast Cancer Family Registry	USA	Case-control study					101	1				
BCINS	Breast Cancer in Northern Israel Study	Israel	Case-control study					724	1334	100	3		
BIGGS	Breast Cancer in Galway Genetic Study	Ireland	Case-control study	719	793	43							
BPC3	Breast and Prostate Cancer Cohort Consortium	International	Prospective cohorts: nested case-control studies									2305	1998
BREOGAN	Breast Oncology Galicia Network	Spain	Case-control study					725	1259	99	19		
BSUCH	Breast Cancer Study of the University of Heidelberg	Germany	Case-control study	951	738	28	5	168	252	1	24		
CBCS	Canadian Breast Cancer Study	Canada	Case-control study					817	568	108			
CCGP	Crete Cancer Genetics Program	Greece	Case-control study					332	665	7			
CECILE	CECILE Breast Cancer Study	France	Case-control study	843	630	93		159	280	26			
CGPS	Copenhagen General Population Study	Denmark	Case-control study	4525	2867	80		716	1408	3			
CNI0-BCS	Spanish National Cancer Centre Breast Cancer Study	Spain	Case-control study	871	866	33							
CPHS	Cancer Prevention Study II Nutrition Cohort	USA	Prospective cohort: nested case-control study	294	138	9	38	3028	2388	597	68		
CTS	California Teachers Study	USA	Prospective cohort: nested case-control study	37	19			610	1156				
DIETCOMPLYF	DietComply Breast Cancer Survival Study	UK	Prospective cohort: nested case-control study					708	3				
EPIC	European Prospective Investigation Into Cancer and Nutrition	International (Europe)	Prospective cohort: nested case-control study					3644	3435	412			
ESTHER	ESTHER Breast Cancer Study	Germany	Case-control study	318	184	1		187	291	3	2		
FHRISK	Family History Risk Study	UK	Case-control study					296	102	25	19		
GC-HBDC	German Consortium for Hereditary Breast & Ovarian Cancer	Germany	Case-control study	139				1593	3416	218		477	634
GENICA	Gene Environment Interaction and Breast Cancer in German	Germany	Case-control study	426	453	9		284	459	1			
GEFAPSIXTO	Randomized phase II trial	Germany	Case-only study					387					
GESCC	Genetic Epidemiology Study of Breast Cancer by Age 50	Germany	Case-control study					181	374	39	7		
HABCS	Hannover Breast Cancer Study	Germany	Case-control study					866	909	19			
HCS	Hospital Clinico San Carlos	Spain	Case-control study					423	3				
HEBCS	Helsinki Breast Cancer Study	Finland	Case-control study	1059	1515	147		177	281			1012	726
HMBCS ²	Hannover-Minsk Breast Cancer Study	Belarus	Case-control study	95	532	2		249	212				
HNBCS	Hannover-Jena Breast Cancer Study	Russia	Case-control study					120	711				
KARBAC	Karolinska Breast Cancer Study	Sweden	Case-control study	658	307			498	5				
KARMA	Karolinska Mammography Project for Risk Prediction of Brea	Sweden	Case-control study					6026	2366	279			
KBPC	Kuopio Breast Cancer Project	Finland	Case-control study	188	22	3		245	522	34			
KCONFAB/AOCS	Kathleen Cunnigham Foundation Consortium for research in Australia and New Zealand	Australia and New Zealand	Case-control study	896	463	68	25						
LMBC	Lieven Multidisciplinary Breast Centre	Belgium	Case-control study					1268	783	22			
MABCS	Macedonian Breast Cancer Study	Macedonia	Case-control study					92	89	1			
MARIE	Mammary Carcinoma Risk Factor Investigation	Germany	Case-control study	1776	1137	154		289	506	6		470	652
MBCSG	Milan Breast Cancer Study Group	Italy	Case-control study	400	188	37	263	366	549	72	167		
MLBCS	Mayo Clinic Breast Cancer Study	USA	Case-control study	1829	1323	253		221	749	167	10		
MCCS	Melbourne Collaborative Cohort Study	Australia	Prospective cohort: nested case-control study					978	861	189			
MCC	Multiethnic Cohort	USA	Prospective cohort: nested case-control study	129	105	25		724	668	5			
MISS	Melanoma Inquiry of Southern Sweden	Sweden	Prospective cohort: nested case-control study					1545	599	102			
MMHS	Mayo Mammography Health Study	USA	Prospective cohort: nested case-control study					1635	275	99	10		
MSKCC	Memorial Sloan-Kettering Cancer Center Study	USA	Case-control study					136	2				
MTLGBCS	Montreal Gene-Environment Breast Cancer Study	Canada	Case-control study	295	192			170	341				
NBCS	Norwegian Breast Cancer Study	Norway	Case-control study	277	1295	9	69						
NBHS	Nashville Breast Health Study	USA	Case-control study	79	89			652	483	112	82		
NC-BCFR	Northern California Breast Cancer Family Registry	USA	Case-control study					151	753	21			
NCBCS	North Carolina Breast Cancer Study	USA	Case-control study					1006	2074	315			
NHS	Nurses Health Study	USA	Prospective cohort: nested case-control study					1804	1103	333	154		
NHS2	Nurses Health Study 2	USA	Prospective cohort: nested case-control study					1905	1112	409	86		
OBCS	Oulu Breast Cancer Study	Finland	Case-control study	414	499	7	1						
OFBCR	Ontario Familial Breast Cancer Registry	Canada	Case-control study	353	487	17		375	1655	9			
ORIGO	Osiden University Medical Centre Breast Cancer Study	Netherlands	Prospective cohort: nested case-control study	326	319	32		560	922	110	21		
PBCS	NCI Polish Breast Cancer Study	Poland	Case-control study	37	27			2045	1740	111	80		
PKARMA	Karolinska Mammography Project for Risk Prediction of Brea	Sweden	Case-control study	5406	4247	436		48	740	94			
PLCO	The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Sc	USA	Prospective cohort: nested case-control study					2595	1822	483			
POSH	Prospective Study of Outcomes in Sporadic Versus Heredita	UK	Case-only study										
PREFACE	Evaluation of Predictive Factors regarding the Effectivity of A	Germany	Case-only study					2981	8				
PROCAS	Predicting the Risk Of Cancer At Screening Study	UK	Prospective cohort: nested case-control study					1656	323	83	241		
RBCS	Rotterdam Breast Cancer Study	Netherlands	Case-control study	688	596	34	2	240	452	22			
SASBAC	Singapore and Sweden Breast Cancer Study	Sweden	Case-control study	1373	1129							756	790
SBCS	Sheffield Breast Cancer Study	UK	Case-control study	848	746	58	39						
SEARCH	Study of Epidemiology and Risk factors in Cancer Heredit	UK	Case-control study	6236	8747	181	64	2673	4057				
SISTER	The Sister Study	USA	Prospective cohort: nested case-control study					1562	1502	496	13		
SKDKFZS	Städtisches Klinikum Karlsruhe Krebsforschungszentrum	Germany	Case-only study	29	134	2			1086	9			
SMC	Swedish Mammography Cohort	Sweden	Prospective cohort: nested case-control study					704	1509				
SUCCESSA	Simultaneous Study of Gemcitabine-Docetaxel Combination	Germany	Case-only study										
SUCCESSC	Simultaneous Study of Docetaxel Based Anthracycline Free A	Germany	Case-only study										
SZBCS	IHCC-Szczecin Breast Cancer Study	Poland	Case-control study	298	325	13	27	174	338	9	40		
TNBCC	Triple-Negative Breast Cancer Consortium	International	Case-control studies	423	475	89			113		507	2890	998
UCIBCS	UCI Breast Cancer Study	USA	Case-control study					258	425	76			
UK2	UK2 GWAS	UK	Case-control study									2663	3628
UKBS	UK Breakthrough Generations Study	UK	Prospective cohort: nested case-control study	327	6	4		705	1048	584			
UKOPS	UK Ovarian Cancer Population Study	UK	Case-control study					974					
USRT	US Radiologic Technologists Study	USA	Case-control study					1699	1354	338			
VUMC												3255	464
WHI	Women's Health Initiative	USA	Prospective cohort: nested case-control study					4617	4930	6			
				37818	35727	2087	535	58383	72000	6501	1624	17588	14910

¹ We excluded the OncoArray data from Norway (the Norwegian Breast Cancer Study) because there were no controls available from Norway

Supplementary Table 2: BCAC studies contributing data to the two-stage model polytomous model investigating for susceptibility SNPs while accounting for heterogeneity according to estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and grade

Acronym	Study Name ^a	Country	Study design	Controls	Estrogen Receptor status			Progesterone Receptor status			HER2 status			Grade			
					ICOGS and Oncoarray Combined ^b			ICOGS and Oncoarray Combined ^b			ICOGS and Oncoarray Combined ^b			ICOGS and Oncoarray Combined ^b			
					Negative	Positive	Unknown	Negative	Positive	Unknown	Negative	Positive	Unknown	1	2	3	Unknown
ZSISTER	The Two Sister Study	USA	Case-only study		185	729	5	230	679	10	695	201	23				919
ABCFS	Australian Breast Cancer Family Study	Australia	Case-control study	738	331	698	410	298	729	412	17	8	1414				1439
ABCS	Amsterdam Breast Cancer Study	Netherlands	Case-control study	1565	227	617	274	320	498	300	512	254	352	135	409	333	241
ABCS-F	Amsterdam Breast Cancer Study – Familial	Netherlands	Case-only study		84	233	684	112	196	693	228	53	720	68	208	164	561
ABCTB	Australian Breast Cancer Tissue Bank	Australia	Case-control study	375	389	553	5	445	495	7	837	88	22	123	293	351	180
AHS	Agricultural Health Study	USA	Prospective cohort: nested case-control study	1137	91	377	45	133	332	48	55	4	454	119	185	153	56
BBC	Bavarian Breast Cancer Cases and Controls	Germany	Case-control study	706	127	698	16	372	428	41	692	101	48	134	431	260	16
BBCS	British Breast Cancer Study	UK	Case-control study	1768	117	557	851	129	296	1100	243	69	1213	146	382	292	705
BCEES	Breast Cancer Employment and Environment Study	Australia	Case-control study	834	116	552	115			783	529	73	181	175	268	146	194
BCFR-NY	New York site of the Breast Cancer Family Registry	USA	Case-control study	27	55	109	237			401			401				401
BCFR-PA	Philadelphia site of the Breast Cancer Family Registry	USA	Case-control study		28	22	13	33	17	13			63	1	4	5	53
BCFR-UTAH	Utah site of the Breast Cancer Family Registry	USA	Case-control study		12	30	59	19	23	59	8	1	92	8	21	20	52
BCINIS	Breast Cancer in Northern Israel Study	Israel	Case-control study	724	233	1080	21	634	678	22	1078	136	120	308	602	296	128
BIGGS	Breast Cancer in Galway Genetic Study	Ireland	Case-control study	49	146	473	164	124	388	271	326	89	368	78	262	210	233
BREOGAN	Breast Oncology Galicia Network	Spain	Case-control study	725	232	985	42	379	831	49	836	216	207	217	622	336	84
BSUCH	Breast Cancer Study of the University of Heidelberg	Germany	Case-control study	1119	210	711	66	278	643	66	680	201	106	118	462	311	96
CBCS	Canadian Breast Cancer Study	Canada	Case-control study	817	108	443	17	147	372	49	359	168	41				568
CCGP	Crete Cancer Genetics Program	Greece	Case-control study	322	177	483	5	199	458	8	532	120	13	49	278	276	62
CECILE	CECILE Breast Cancer Study	France	Case-control study	1002	133	756	21	253	626	31	716	112	82				910
CGPS	Copenhagen General Population Study	Denmark	Case-control study	5241	565	3006	704	853	1716	1706	1537	515	2223	875	1357	577	1466
CNIO-BCS	Spanish National Cancer Centre Breast Cancer Study	Spain	Case-control study	829	97	310	343	163	256	331	201	108	441	65	108	120	457
CPSII	Cancer Prevention Study-II Nutrition Cohort	USA	Prospective cohort: nested case-control study	3322	74	1960	492	398	1569	559	830	129	1567	598	1011	502	415
CTS	California Teachers Study	USA	Prospective cohort: nested case-control study	630	194	981		100	1075		100	1075		368	508	267	32
DIETCOMPLY	DietComply Breast Cancer Survival Study	UK	Prospective cohort: nested case-control study		108	596	4	145	335	228	353	111	244	111	325	269	3
EPIC	European Prospective Investigation Into Cancer and Nutrition	International (Europe)	Prospective cohort: nested case-control study	3597	181	2004	1250	511	1349	1575	856	206	2373	361	998	658	1418
ESTHER	ESTHER Breast Cancer Study	Germany	Case-control study	505	99	305	71	137	262	76	130	51	294	30	217	198	30
FHRISK	Family History Risk Study	UK	Case-control study		6	43	53	12	37	53	33	5	64	17	29	51	5
GC-HBOC	German Consortium for Hereditary Breast & Ovarian Cancer	Germany	Case-control study	1732	389	1149	1878	419	1109	1888	863	209	2344	250	1379	875	912
GENICA	Gene Environment Interaction and Breast Cancer in Germany	Germany	Case-control study	710	191	712	9	264	638	10	465	184	263	78	531	280	23
GEPARSIXTO	Randomized phase II trial	Germany	Case-only study		274	112		316	70		208	178		7	137	242	
GESBC	Genetic Epidemiology Study of Breast Cancer by Age 50	Germany	Case-control study	181	110	177	25	119	166	27			312	23	156	119	14
HABCS	Hannover Breast Cancer Study	Germany	Case-control study	863	158	653	98	196	602	111	132	19	758	64	388	272	185
HCSC	Hospital Clinico San Carlos	Spain	Case-control study		107	289	27	147	241	35	223	92	108	29	251	92	51
HEBCS	Helsinki Breast Cancer Study	Finland	Case-control study	1236	288	1465	43	579	1170	47	862	156	778	479	787	452	78
HUBCS	Hannover-Ufa Breast Cancer Study	Russia	Case-control study	116	17	34	160	22	29	160	28	22	161	17	68	38	88
KARBAC	Karolinska Breast Cancer Study	Sweden	Case-control study		73	363	367	99	279	425	26	5	772	112	199	111	381
KARMA	Karolinska Mammography Project for Risk Prediction of Breast Cancer – Cohort Study	Sweden	Case-control study	6026	171	1293	902	355	1062	949	1099	171	1096	286	622	424	1034
KBCP	Kuopio Breast Cancer Project	Finland	Case-control study	433	116	375	53	151	262	131	381	102	61	127	221	130	66
KCONFAB/AI	Kathleen Cuningham Foundation Consortium for research into Familial Breast Cancer/Australian Ovarian Cancer Study	Australia and New Zealand	Case-control study	896	73	210	180	76	177	210	79	30	354	84	132	131	116
LMBC	Leuven Multidisciplinary Breast Centre	Belgium	Case-control study	1268	142	641		215	564	4	649	101	33	123	352	308	
MABCS	Macedonian Breast Cancer Study	Macedonia	Case-control study	90	17	69	3	26	45	18	52	19	18	3	28	41	17
MARIE	Mammary Carcinoma Risk Factor Investigation	Germany	Case-control study	2065	362	1274	7	551	1084	8	1215	281	147	338	808	476	21
MBCSG	Milan Breast Cancer Study Group	Italy	Case-control study	766	105	351	281	142	313	282	234	121	382	46	189	189	313
MCBCS	Mayo Clinic Breast Cancer Study	USA	Case-control study	2041	314	1713	45	519	1496	57	1497	277	298	572	903	532	65
MCCS	Melbourne Collaborative Cohort Study	Australia	Prospective cohort: nested case-control study	1206	203	705	150	312	594	152	738	112	208	182	431	296	149
MEC	Multiethnic Cohort	USA	Prospective cohort: nested case-control study	853	95	582	96	161	481	131	89	25	659	209	319	170	75
MISS	Melanoma Inquiry of Southern Sweden	Sweden	Prospective cohort: nested case-control study	1529	75	352	172	137	295	167	312	30	257	9	14	5	571
MMHS	Mayo Mammography Health Study	USA	Prospective cohort: nested case-control study	1635	33	238	4	64	207	4	223	20	32	83	116	54	22
MSKCC	Memorial Sloan-Kettering Cancer Center Study	USA	Case-control study		136			136			136						136
MTLGEBCS	Montreal Gene-Environment Breast Cancer Study	Canada	Case-control study	465	66	460	7	132	393	8	457	54	22				533
NBCS	Norwegian Breast Cancer Study	Norway	Case-control study	271	273	879	78	428	713	89	816	95	319	181	435	267	347
NBHS	Nashville Breast Health Study	USA	Case-control study	731	258	256	58	294	216	62	340	121	111				572
NC-BCFR	Northern California Breast Cancer Family Registry	USA	Case-control study	150	246	396	111	248	393	112	185	18	550	94	247	284	128
NCBCS	North Carolina Breast Cancer study	USA	Case-control study	1006	495	1457	122	618	1262	194	1536	283	255	395	603	510	566
NHS	Nurses Health Study	USA	Prospective cohort: nested case-control study	1804	167	827	109	307	662	134	503	77	523	207	370	248	278
NHS2	Nurses Health Study 2	USA	Prospective cohort: nested case-control study	1905	190	868	54	292	753	67	665	137	310	243	458	316	95
OBCS	Oulu Breast Cancer Study	Finland	Case-control study	414	96	403		143	355	1	430	69		86	215	182	16
OFBCR	Ontario Familial Breast Cancer Registry	Canada	Case-control study	728	525	1170	447	616	1050	476	549	81	1512	373	640	594	535
ORIGO	Leiden University Medical Centre Breast Cancer Study	Netherlands	Prospective cohort: nested case-control study		294	744	202	317	474	449	117	59	1064	158	396	357	329
PBCS	NCI Polish Breast Cancer Study	Poland	Case-control study	2082	529	1079	159	756	846	165	984	211	572	334	843	433	157
PKARMA	Karolinska Mammography Project for Risk Prediction of Breast Cancer - Case-Control Study	Sweden	Case-control study	5454	693	3786	508	1311	3087	589	1061	162	3764	622	1615	873	1877
PLCO	The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial	USA	Prospective cohort: nested case-control study	2595	220	1372	230	388	1139	295	1021	136	665	511	753	401	157
POSH	Prospective Study of Outcomes in Sporadic Versus Hereditary Breast Cancer	UK	Case-only study		222	861	5	241	584	263	152	128	808	82	422	559	25

Supplementary Table 3: CIMBA studies contributing data on *BRCA1* mutation carriers, by genotyping initiative

Acronym	Study Name	Country	OncoArray		iCOGS	
			Unaffected	Breast cancer	Unaffected	Breast cancer
BCFR-AU	Australian site of the Breast Cancer Family Registry	AUSTRALIA	13	25	0	2
BCFR-NC	Northern California site of the Breast Cancer Family Registry	USA	3	12	1	1
BCFR-NY	New York site of the Breast Cancer Family Registry	USA	24	37	4	5
BCFR-ON	Ontario site of the Breast Cancer Family Registry	CANADA	34	86	2	7
BCFR-PA	Philadelphia site of the Breast Cancer Family Registry	USA	26	17	14	16
BCFR-UT	Utah site of the Breast Cancer Family Registry	USA	135	64	1	0
BFBOCC	Baltic Familial Breast Ovarian Cancer Consortium	LITHUANIA/L ATVIA	133	111	16	8
BIDMC	Beth Israel Deaconess Medical Center	USA	41	44	1	1
BMBSA	BRCA-gene mutations and breast cancer in South African women	SOUTH AFRICA	21	37	2	1
BRICOH	Beckman Research Institute of the City of Hope	USA	96	50	11	9
CBCS	Rigshospitalet	DENMARK	110	75	80	57
CNIO	Spanish National Cancer Centre	SPAIN	32	31	49	44
COH	City of Hope Cancer Center	USA	84	141	6	8
CONSTIT TEAM	CONsorzio Studi Italiani sui Tumori Ereditari Alla Mammella	ITALY	265	271	217	234
DEMOKRITOS	National Centre for Scientific Research Demokritos	GREECE	85	132	12	20
DFCI	Dana-Farber Cancer Institute	USA	82	65	3	4
DKFZ	German Cancer Research Center	GERMANY	19	36	0	2
EMBRACE	Epidemiological Study of Familial Breast Cancer	UK/IRELAND	907	785	14	13
FCCC	Fox Chase Cancer Center	USA	49	26	20	19
FPGMX	Fundación Pública Galega de Medicina Xenómica	SPAIN	40	61		
GC-HBOC	German Familial Breast Group	GERMANY	673	1145	54	111
GEMO	Genetic Modifiers of cancer risk in <i>BRCA1/2</i> mutation carriers	FRANCE/USA	630	842	114	111
GEORGETOWN	Georgetown University	USA	6	5	1	2
G-FAST	Ghent University Hospital	BELGIUM	69	121	91	42
HCSC	Hospital Clinico San Carlos	SPAIN	85	55	5	6
HEBCS	Helsinki Breast Cancer Study	FINLAND	67	53	3	5
HEBON	Genen Omgeving studie van de werkgroep Hereditair Borstkanker Onderzoek Nederland	NETHERLAND S	500	372	220	202
HUNBOCS	Molecular Genetic Studies of Breast- and Ovarian Cancer in Hungary	HUNGARY	101	179		
HVH	University Hospital Vall d'Hebron	SPAIN	56	62	0	1
ICO	Institut Català d'Oncologia	SPAIN	150	130	5	1
IHCC	International Hereditary Cancer Centre	POLAND	121	77	279	223
INHERIT	INterdisciplinary HEalth Research Internal Team BREast CANcer susceptibility	CANADA (QUEBEC)	52	37	6	2
IOVHBOCS	Istituto Oncologico Veneto	ITALY	93	111	5	4
IPOBCS	Portuguese Oncology Institute-Porto Breast Cancer Study	PORTUGAL	79	36	1	2
KCONFAB	Kathleen Cuninghame Consortium for Research into Familial Breast Cancer	AUSTRALIA	355	366	24	26
KUMC	University of Kansas Medical Center	USA	3	11		
MAYO	Mayo Clinic	USA	126	121	12	10
MCGILL	McGill University	CANADA (QUEBEC) CZECH	30	24		
MODSQUAD	Modifier Study of Quantitative Effects on Disease	REPUBLIC			68	106
MSKCC	Memorial Sloane Kettering Cancer Center	USA	193	185	32	59
MUV	General Hospital Vienna	AUSTRIA	266	268	11	11

NAROD	Women's College Research Institute Hereditary Breast and Ovarian Cancer Study	CANADA			100	46
NCI	National Cancer Institute	USA	108	42	6	1
NNPIO	N.N. Petrov Institute of Oncology	RUSSIA	22	44	1	4
NORTHSHORE	NorthShore University HealthSystem	USA	40	40		
NRG_ONCOLOGY	NRG Oncology	USA/AUSTRA				
OCGN	Ontario Cancer Genetics Network	LIA	153	166	4	7
OSU CCG	The Ohio State University Comprehensive Cancer Center	CANADA	133	71	6	4
OUH	Odense University Hospital	USA	34	39	8	10
PBCS	Università di Pisa	DENMARK	358	192	10	10
SMC	Sheba Medical Centre	ITALY	39	49	6	5
SWE-BRCA	Swedish Breast Cancer Study	ISRAEL	99	65	57	41
UCHICAGO	University of Chicago	SWEDEN	237	188	52	38
UCSF	University of California San Francisco	USA	51	43	7	0
UKGRFOCR	UK and Gilda Radner Familial Ovarian Cancer Registries	USA	60	32	16	15
UPENN	University of Pennsylvania	UK	40	13	5	0
UPITT	Cancer Family Registry University of Pittsburg	USA	218	239	11	22
UTMDACC	University of Texas MD Anderson Cancer Center	USA	77	77		
VFCTG	Victorian Familial Cancer Trials Group	USA	18	25	27	45
WCP	Women's Cancer Program at Cedars-Sinai Medical Center	AUSTRALIA	104	103	2	1
		USA	137	50	10	6
			7782	7784	1712	1630

Supplementary Table 4: BCAC studies and CIMBA *BRCA1* mutation carriers sample size compared with previous publication

Previous and current BCAC studies	BCAC						CIMBA <i>BRCA1</i> mutation carriers			
	iCOGS		OncoArray		Other GWAS		iCOGS		OncoArray	
	Control	Cases	Control	Cases	Control	Cases	Unaffected	Cases	Control	Cases
Michailidou et al. Nature 551, no. 7678 (2017)	42892	46785	45494	61282	14910	17588				
Milne et al. Nat Genet 49, 1767-1778 (2017) ¹	42468	7333	45494	9655			1712	1630	7782	7784
Data in overall analysis ²	37818	38349	58383	80125	14910	17588				
Data in subtypes analysis ³	37628	34783	56779	71708						
CIMBA-BCAC TN meta-analys ⁴	37628	2,057	56779	5,121			1712	1630	7782	7784

¹ Milne et al. Nat Genet 49, 1767-1778 (2017) restricted to cases with estrogen receptor negative breast cancer

² Compared to Michailidou et al. Nature 551, no. 7678 (2017), 5,074 controls and 8,436 cases originally genotyped by iCOGS were regenotyped by OncoArray

³ Subtype analyses of BCAC data restricted to invasive breast cancer cases and subjects with age information

⁴ The effective sample (see **Supplementary Note**) of BCAC triple-negative cases as a result of the EM algorithm are 8,602 for iCOGS and OncoArray together

Supplementary Table 5: Twenty-two variants identified using standard logistic regression (n = 133,384 cases, n = 113,789 controls).

Lead variant ¹	Chr. 2	Position	Alleles ³	MAF ⁴	Imputation Quality iCOGS/ONCO ⁵	OR ⁶	95%CI ⁷	P-value ⁸	P-value (Michailidou et al) ⁹
rs5776993	1	110,222,901	C/CA	0.12	0.70/0.82	0.95	0.92-0.96	2.6 x 10 ⁻⁸	2.0 x 10 ⁻⁷
rs9712235	2	67,881,757	A/G	0.26	0.86/1.00	1.04	1.02-1.05	4.8 x 10 ⁻⁸	7.2 x 10 ⁻⁷
rs4602255	2	69,392,128	G/A	0.45	1.00/1.00	1.04	1.02-1.05	2.0 x 10 ⁻⁹	1.2 x 10 ⁻⁷
rs1375631	3	16,778,867	G/A	0.5	1.00/1.00	0.97	0.95-0.98	6.8 x 10 ⁻⁹	2.0 x 10 ⁻⁷
rs2886671	3	59,373,745	C/T	0.43	0.63/1.00	0.97	0.95-0.98	4.3 x 10 ⁻⁸	6.9 x 10 ⁻⁷
rs34052812	3	156,535,958	A/AT	0.33	0.94/0.94	0.96	0.95-0.98	3.3 x 10 ⁻⁸	8.1 x 10 ⁻⁷
rs7760611	6	21,903,533	C/T	0.47	1.00/1.00	0.96	0.95-0.98	1.5 x 10 ⁻⁹	3.2 x 10 ⁻⁷
rs188092014	7	74,341,926	G/C	0.19	0.67/0.83	1.05	1.03-1.07	2.0 x 10 ⁻⁸	1.5 x 10 ⁻⁶
rs79518236	7	98,026,554	ACT/A	0.23	1.00/1.00	0.96	0.95-0.97	6.6 x 10 ⁻⁹	1.0 x 10 ⁻⁷
rs142890050	8	23,480,253	C/CTT	0.46	0.97/0.96	0.97	0.95-0.98	3.5 x 10 ⁻⁸	6.7 x 10 ⁻⁸
rs13256025	8	25,831,778	C/T	0.2	0.68/1.00	1.05	1.03-1.06	1.4 x 10 ⁻⁸	2.1 x 10 ⁻⁷
rs13277568	8	116,679,547	A/G	0.37	0.85/1.00	0.97	0.95-0.98	2.2 x 10 ⁻⁸	7.6 x 10 ⁻⁷
rs4742903	9	106,856,793	C/G	0.44	1.00/1.00	0.97	0.96-0.98	2.6 x 10 ⁻⁸	1.8 x 10 ⁻⁷
rs10838267	11	44,368,892	A/G	0.45	0.99/0.99	0.97	0.96-0.98	4.5 x 10 ⁻⁸	3.2 x 10 ⁻⁷
12:29140260 ¹⁰	12	29,140,260	A/G	0.09	0.93/1.00	0.93	0.91-0.95	7.7 x 10 ⁻¹²	3.0 x 10 ⁻¹⁰
rs11065822	12	111,600,134	G/T	0.37	0.88/1.00	0.96	0.95-0.98	5.9 x 10 ⁻⁹	9.2 x 10 ⁻⁸
rs1061657 ¹⁰	12	115,108,136	T/C	0.26	0.97/1.00	1.04	1.03-1.06	2.5 x 10 ⁻¹⁰	1.4 x 10 ⁻⁹
rs11652463	17	70,405,095	C/G	0.31	0.76/0.84	0.96	0.95-0.97	4.2 x 10 ⁻⁸	8.4 x 10 ⁻⁸
rs12962334	18	20,477,934	C/G	0.32	0.99/1.00	1.04	1.03-1.05	3.8 x 10 ⁻⁹	9.6 x 10 ⁻⁷
rs17743054 ¹⁰	18	42,900,892	T/C	0.28	1.00/1.00	0.96	0.95-0.97	1.5 x 10 ⁻¹⁰	2.2 x 10 ⁻¹⁰
rs13039563	20	52,296,849	G/A	0.24	1.00/0.95	1.04	1.03-1.06	3.1 x 10 ⁻⁹	2.1 x 10 ⁻⁷
rs9808759	21	47,780,223	C/T	0.07	0.99/0.98	1.07	1.05-1.09	5.8 x 10 ⁻⁹	4.0 x 10 ⁻⁷

¹ Showing the strongest signal in each region

² Chr., chromosome

³ Major alleles listed first

⁴ MAF, minor allele frequency

⁵ Imputation quality (r^2) for iCOGS/OncoArray

⁶ OR, odds ratio per copy of the minor allele

⁷ 95% CI, 95% confidence interval

Supplementary Table 6: Sixteen variants identified using two-stage polytomous logistic regression (n = 106,278 invasive cases, n = 91,477 controls), eight of them were also identified in overall analysis.

Lead variant ¹	Chr. ²	Position	Alleles ³	MAF ⁴	Imputation Quality	iCOGS/ONCO ⁵	Mixed effect model global association test P ⁶	Fixed effect model global association test P ⁷	Global heterogeneity test P ⁸
1:145126177	1	145,126,177	G/A	0.04		0.48/0.65	9.6 × 10 ⁻⁹	4.0 × 10 ⁻⁸	2.8 × 10 ⁻⁶
rs495367	4	1,986,972	A/G	0.35		0.67/0.79	2.2 × 10 ⁻⁸	2.9 × 10 ⁻⁷	5.8 × 10 ⁻²
rs138044103	5	67,424,121	C/CTG	0.45		0.92/1.00	2.4 × 10 ⁻⁹	4.7 × 10 ⁻⁹	5.2 × 10 ⁻⁷
rs7924772	11	120,233,626	A/G	0.39		0.65/1.00	3.2 × 10 ⁻⁵	3.6 × 10 ⁻⁸	1.4 × 10 ⁻³
rs78378222	17	7,571,752	T/G	0.01		0.90/1.00	1.8 × 10 ⁻⁹	1.3 × 10 ⁻¹⁰	9.1 × 10 ⁻⁸
rs206435	18	10,354,649	C/A	0.5		1.00/0.99	1.6 × 10 ⁻⁷	3.5 × 10 ⁻⁸	1.1 × 10 ⁻⁹
rs141526427	20	11,502,618	A/AAC	0.25		0.76/0.95	2.6 × 10 ⁻⁸	5.8 × 10 ⁻⁸	6.2 × 10 ⁻⁵
rs6065254	20	39,248,265	G/A	0.39		0.89/0.97	1.8 × 10 ⁻⁹	2.3 × 10 ⁻⁹	7.3 × 10 ⁻⁷
rs9712235 ⁹	2	67,881,757	A/G	0.26		0.86/1.00	2.0 × 10 ⁻⁷	1.4 × 10 ⁻⁸	6.7 × 10 ⁻³
rs7760611 ⁹	6	21,903,533	C/T	0.47		1.00/1.00	1.7 × 10 ⁻⁹	3.6 × 10 ⁻⁹	1.4 × 10 ⁻³
rs79518236 ⁹	7	98,026,554	ACT/A	0.23		1.00/1.00	1.7 × 10 ⁻⁸	3.9 × 10 ⁻¹⁰	1.6 × 10 ⁻³
12:29140260 ⁹	12	29,140,260	A/G	0.09		0.93/1.00	4.3 × 10 ⁻⁹	1.1 × 10 ⁻⁸	3.9 × 10 ⁻¹
rs1061657 ⁹	12	115,108,136	T/C	0.26		0.97/1.00	6.1 × 10 ⁻⁹	9.3 × 10 ⁻⁹	6.1 × 10 ⁻²
rs12962334 ⁹	18	20,477,934	C/G	0.32		0.99/1.00	4.2 × 10 ⁻⁸	1.5 × 10 ⁻⁷	4.4 × 10 ⁻²
rs17743054 ⁹	18	42,900,892	T/C	0.28		1.00/1.00	1.8 × 10 ⁻⁸	3.9 × 10 ⁻⁸	1.9 × 10 ⁻²
rs13039563 ⁹	20	52,296,849	G/A	0.24		1.00/0.95	1.4 × 10 ⁻⁹	3.9 × 10 ⁻⁹	4.9 × 10 ⁻³

¹ Variants were selected based on either the two-stage mixed effect model or the two-stage fixed effect model global association

² Chr., chromosome

³ Major alleles listed first

⁴ MAF, minor allele frequency

⁵ Imputation quality (r²) for iCOGS/OncoArray

⁶ Mixed effect two-stage polytomous model adjusted for top 10 PCs and age while accounting subtypes heterogeneity for ER (fixed effect), PR (random effect), HER2(random effect), and grade (random effect). G

⁷ Fixed effect two-stage model adjusted for top 10 PCs and age while accounting for ER, PR, HER2 and grade all as fixed effects

⁸ The global test for heterogeneity was performed under the mixed-effect model tests if variants show evidence of heterogeneity with respect to any of the underlying tumor markers, ER, PR, HER2 and/or grade

⁹ Variants were also detected in the overall breast cancer analysis.

Supplementary Table 10: Conditional analysis of one genome-wide significant variant from meta-analysis of triple negative breast cancer of BCAC and CIMBA *B/*

Lead variant ¹	Chr. ²	Position	MAF ³	Nearby known variant ⁴	LD ⁵	D' ⁶	Meta-analysis P ⁷	Conditional analysis P ⁸
rs2464195 ⁹	12	121,435,475	0.37	rs206966	0	0	2.5 x 10 ⁻⁸	2.2 x 10 ⁻⁸

¹ Showing the strongest signal in each region

² Chr., chromosome

³ MAF, minor allele frequency

⁴ Known variantss previous published in Michailidou et al. Nature 551, no. 7678 (2017) and Milne et al. Nat Genet 49, 1767-1778 (2017)

⁵ LD, linkage disequilibrium between lead variant and nearby known variant estimated from European-ancestry controls in OncoArray

⁶ D', D prime between lead variant and nearby known variant estimated from European-ancestry controls in OncoArray

⁷ Meta-analysis using triple negative from BCAC and BRACA1 mutation carriers from CIMBA

⁸ Meta-analysis p-value conditional on the nearby known variants, p-value threshold of $p < 1 \times 10^{-6}$ was used for conditional analyses (reason described in [Online Me](#)

⁹ Conditionally significant after adjusting for nearby known variant

CA1 mutation carriers data on nearby (within +/- 2 MB) known breast cancer variant BCAC: n = 8,602 effective triple-negative cases, n = 91,477 contr

thods). P-values are raw p-values from two-tailed z-test statistics.

ols; CIMBA BRCA1 carriers: n = 9,414 cases, n = 9,494 controls)

Supplementary Table 1: Association of the 32 variants with intrinsic-like subtypes, comparing results restricted to cases with complete tumor marker data and results from implementing the EM algorithm for missing tumor marker data. Odds ratio and 95% confidence intervals estimated from the fixed-effect two-stage model.

Variant	Chr ^a	Pos ^b	Major/Minor Alleles ^c	MAF ^d	Case-control intrinsic-like odds ratios ^e																										
					Results restricted to cases with complete tumor marker data ^f			Results implementing EM algorithm for missing tumor marker data ^g			Results restricted to cases with complete tumor marker data ^f			Results implementing EM algorithm for missing tumor marker data ^g			Results restricted to cases with complete tumor marker data ^f			Results implementing EM algorithm for missing tumor marker data ^g											
					Luminal A-like OR	Luminal B-like 95% CI	Luminal A-like p-value ^h	Luminal A-like OR	Luminal A-like 95% CI	p-value ^h	Luminal B-like OR	HER2-negative-like 95% CI	HER2-enriched-like p-value ^h	Luminal B-like OR	Luminal B-like 95% CI	HER2-negative-like p-value ^h	Luminal B-like OR	Luminal B-like 95% CI	HER2-enriched-like p-value ^h	HER2-enriched-like OR (95% CI)	HER2-enriched-like 95% CI	HER2-enriched-like p-value ^h	HER2-enriched-like OR	HER2-enriched-like 95% CI	HER2-enriched-like p-value ^h	Triple-negative OR	Triple-negative 95% CI	Triple-negative p-value ^h	Triple-negative OR (95% CI)	Triple-negative 95% CI	Triple-negative p-value ^h
r37/6993	1	11022205	C/GA	0.117	0.97	0.89-1.06	5.40E-03	0.94	0.91-0.96	9.85E-07	0.97	0.91-1.03	1.12E-01	0.97	0.91-1.02	2.56E-01	0.93	0.90-0.96	1.88E-05	0.94	0.89-0.99	1.18E-02	0.92	0.87-0.98	9.23E-03	0.95	0.87-1.03	3.07E-01	0.96	0.91-1.01	1.11E-05
r93/2225	2	67821757	A/G	0.258	1.02	0.96-1.08	5.97E-01	1.04	1.01-1.04	6.98E-04	1.00	0.96-1.06	8.96E-01	1.00	0.96-1.04	9.14E-01	1.00	0.99-1.06	1.90E-01	1.01	0.97-1.05	6.27E-01	1.02	0.96-1.08	5.99E-01	1.07	1.03-1.11	7.94E-04	1.09	1.05-1.12	1.95E-06
r400225	2	69392128	G/A	0.96	0.96	1.01-1.12	2.07E-02	1.03	1.01-1.04	6.98E-04	1.03	0.99-1.06	1.64E-01	1.02	1.00-1.04	2.81E-02	1.05	1.02-1.08	2.87E-03	1.05	1.02-1.08	1.10E-02	1.07	1.02-1.08	1.10E-02	1.07	1.02-1.13	7.76E-03	1.09	1.05-1.16	3.92E-03
r1317501	3	16717801	G/A	0.495	0.99	0.94-1.04	6.58E-03	0.97	0.95-0.98	4.23E-05	0.98	0.94-1.01	2.01E-01	0.98	0.95-1.01	2.81E-01	0.96	0.94-0.98	5.62E-05	0.99	0.96-1.02	5.13E-01	1.00	0.96-1.03	7.93E-01	0.96	0.93-1.02	1.17E-01	0.95	0.92-0.97	2.33E-04
r2086611	3	15931348	C/T	0.617	0.99	0.93-1.00	4.43E-02	0.96	0.94-0.98	1.47E-06	0.98	0.95-1.02	8.82E-01	0.99	0.96-1.03	4.54E-01	0.96	0.94-0.98	6.35E-05	0.95	0.92-0.98	1.37E-03	0.94	0.90-0.99	1.16E-02	0.97	0.94-1.01	1.04E-01	0.97	0.94-1.00	7.88E-02
r34052812	3	15651994	A/A*	0.312	0.97	0.91-1.02	2.45E-01	0.96	0.94-0.97	3.94E-07	0.97	0.91-1.00	8.60E-02	0.96	0.93-1.00	4.54E-02	0.96	0.94-0.98	3.64E-05	0.95	0.92-0.98	2.56E-03	0.98	0.94-1.02	2.93E-01	0.97	0.92-1.02	2.65E-01	0.98	0.94-1.01	1.98E-01
r7170561	6	21851233	C/T	0.455	1.01	0.96-1.07	6.69E-02	0.96	0.94-0.97	1.35E-07	0.94	0.90-0.97	4.86E-04	0.94	0.91-0.97	2.81E-04	0.96	0.94-0.99	3.54E-05	0.96	0.94-0.99	1.13E-02	0.97	0.94-1.01	2.18E-01	1.02	0.98-1.05	3.34E-01	1.08	0.98-1.04	7.30E-03
r74300214	7	74304216	G/C	0.202	1.1	1.01-1.19	2.02E-02	1.05	1.03-1.07	6.22E-05	1.03	0.98-1.08	2.60E-01	1.03	1.00-1.06	2.01E-02	1.04	0.99-1.08	9.34E-02	1.04	0.99-1.09	1.28E-01	1.07	1.00-1.10	1.28E-01	1.04	0.99-1.10	8.32E-02	1.05	1.01-1.09	2.61E-02
r75218236	7	9802854	A/C	0.215	0.98	0.92-1.04	5.22E-01	0.96	0.94-0.98	6.64E-05	0.93	0.89-0.97	1.36E-03	0.92	0.89-0.96	2.20E-04	0.93	0.90-0.96	7.33E-05	0.94	0.91-0.99	8.67E-03	0.97	0.92-1.03	4.02E-01	0.98	0.95-1.03	4.61E-01	0.97	0.94-1.01	1.20E-02
r13269050	8	23481021	C/C	0.425	0.99	0.94-1.04	6.99E-01	0.96	0.94-0.97	6.66E-08	0.96	0.92-0.99	2.92E-02	0.96	0.92-0.99	1.41E-02	0.96	0.94-0.98	6.29E-01	1.00	0.97-1.04	5.48E-01	0.99	0.96-1.04	5.68E-01	0.97	0.94-1.01	3.96E-01	0.97	0.94-1.00	3.97E-02
r1325625	8	2981777	C/T	0.187	1.07	1.00-1.15	4.41E-02	1.09	1.03-1.07	2.37E-04	1.03	0.98-1.08	2.08E-01	1.03	0.98-1.08	2.13E-01	1.06	1.01-1.08	1.79E-05	1.05	1.01-1.10	5.90E-03	1.04	1.00-1.09	6.49E-02	1.09	1.02-1.16	1.08E-02	1.02	0.98-1.07	3.23E-01
r13277568	8	11667954	A/G	0.349	0.98	0.93-1.04	4.94E-01	0.96	0.94-0.98	9.68E-03	1.00	0.97-1.04	8.23E-01	0.99	0.96-1.03	7.95E-01	0.97	0.95-0.99	1.87E-03	0.95	0.92-0.98	1.10E-03	0.99	0.95-1.03	9.09E-01	1.00	0.96-1.03	4.91E-01	1.00	0.97-1.03	9.61E-02
r4542493	9	10586791	C/G	0.445	0.97	0.92-1.03	3.08E-01	0.99	0.97-1.00	8.26E-02	0.92	0.89-0.95	6.18E-06	0.92	0.89-0.95	6.47E-06	0.92	0.89-0.95	6.54E-03	0.96	0.93-1.00	3.10E-02	0.96	0.93-1.00	3.07E-01	0.95	0.92-0.98	1.65E-03	0.96	0.93-0.99	3.18E-03
r13388887	11	4483899	A/G	0.449	0.99	0.94-1.05	7.93E-01	0.97	0.95-0.98	3.88E-06	0.97	0.94-1.01	1.07E-01	0.96	0.93-0.99	2.99E-02	0.97	0.95-0.99	2.96E-03	0.96	0.93-0.98	3.04E-04	0.95	0.92-0.99	5.68E-03	1.00	0.95-1.05	8.78E-01	0.96	0.93-1.00	6.48E-02
r132_2140240	12	2694026	A/G	0.055	0.9	0.81-0.99	3.65E-02	0.91	0.89-0.94	3.57E-10	0.93	0.87-1.00	4.06E-02	0.93	0.88-0.99	3.54E-02	0.93	0.89-0.96	7.51E-05	0.96	0.91-1.01	1.15E-01	0.94	0.88-1.00	5.38E-02	0.90	0.82-0.99	2.45E-02	0.95	0.90-1.01	9.35E-02
r132_11500134	12	11500134	G/T	0.383	0.97	0.92-1.03	3.11E-01	0.97	0.95-0.98	2.98E-05	0.97	0.94-1.01	1.48E-01	0.97	0.94-1.01	1.45E-01	0.95	0.92-0.98	1.71E-03	0.95	0.92-0.98	6.03E-03	0.96	0.92-0.99	1.11E-01	0.97	0.94-1.01	9.33E-02	0.96	0.93-0.99	1.97E-02
r132_11500136	12	11500136	T/C	0.273	0.98	0.93-1.05	6.26E-01	1.05	1.03-1.07	9.55E-08	1.03	0.96-1.07	1.89E-01	1.04	1.01-1.08	3.87E-06	1.07	1.03-1.10	1.02E-04	1.05	1.02-1.09	2.31E-02	1.09	1.04-1.09	7.96E-01	1.01	0.97-1.05	3.79E-01	1.02	0.97-1.05	2.71E-04
r13152863	17	7046509	C/G	0.322	0.96	0.90-1.02	2.11E-01	0.97	0.95-0.99	5.82E-04	0.95	0.91-0.99	1.15E-02	0.96	0.92-1.00	3.02E-02	0.97	0.94-0.99	4.45E-03	0.95	0.92-0.99	1.03E-02	0.94	0.90-0.98	2.00E-03	0.95	0.89-1.01	8.98E-02	0.94	0.90-0.98	2.88E-03
r13292154	18	2047794	C/G	0.307	1.05	0.99-1.11	9.44E-02	1.04	1.01-1.06	3.03E-03	1.03	0.99-1.07	2.80E-01	1.03	0.99-1.07	2.29E-01	1.04	1.01-1.06	2.23E-04	1.06	1.02-1.09	6.15E-04	1.06	1.02-1.10	5.37E-03	1.05	1.00-1.11	5.93E-02	1.05	0.98-1.05	4.24E-03
r13274854	18	4290892	T/C	0.283	1.02	0.97-1.09	4.16E-01	0.95	0.93-0.97	1.78E-08	0.94	0.91-0.98	5.03E-03	0.95	0.92-0.99	1.49E-08	0.97	0.94-1.00	7.92E-02	0.95	0.92-0.99	1.61E-02	1.02	0.96-1.08	5.05E-01	0.97	0.93-1.01	1.23E-01	0.96	0.93-0.99	1.41E-02
r13289963	20	5226864	G/A	0.249	1.01	0.95-1.07	8.06E-01	1.08	1.04-1.08	4.93E-10	1.05	1.01-1.10	1.39E-02	1.06	1.02-1.10	5.36E-03	1.07	1.03-1.09	3.17E-02	1.04	1.01-1.09	2.17E-02	1.07	0.94-1.06	9.94E-01	1.00	0.94-1.06	9.36E-01	1.00	0.94-1.04	9.44E-03
r9808759	21	4778022	C/T	0.07	0.99	0.90-1.10	9.96E-01	1.08	1.05-1.11	1.65E-02	1.06	0.99-1.13	1.12E-01	1.07	1.01-1.14	9.31E-04	1.07	1.01-1.13	1.18E-02	1.04	0.98-1.12	2.00E-01	1.07	0.98-1.12	5.08E-01	1.07	1.01-1.14	2.11E-02	1.09	1.04-1.16	1.46E-03
r145126177	24	145126177	A/G	0.037	0.92	0.77-1.10	3.75E-01	1.15	1.10-1.21	7.24E-09	0.96	0.89-1.08	4.90E-01	0.97	0.86-1.08	5.75E-01	1.11	1.01-1.19	5.07E-04	0.96	0.87-1.05	3.79E-01	0.97	0.86-1.09	6.09E-01	0.94	0.79-1.11	7.42E-01	1.01	0.92-1.11	8.39E-03
r454361	4	6986972	A/G	0.945	1.06	0.99-1.13	8.78E-02	1.05	1.03-1.07	1.99E-02	1.05	1.01-1.07	2.74E-02	1.05	1.01-1.06	1.08E-02	1.04	1.01-1.06	1.15E-03	1.04	1.00-1.09	6.00E-02	1.06	1.00-1.13	4.45E-02	0.99	0.95-1.03	6.36E-01	1.00	0.97-1.04	8.55E-04
r13804103	5	6744121	C/G	0.46	1.01	0.96-1.07	6.12E-01	1.05	1.03-1.07	1.02E-09	1.04	1.00-1.08	2.85E-02	1.03	1.00-1.07	5.52E-05	1.06	1.04-1.08	2.98E-08	0.99	0.96-1.01	3.20E-01	0.98	0.95-1.02	3.21E-01	1.00	0.97-1.04	8.80E-01	0.98	0.95-1.01	1.59E-01
r13204719	11	32023026	A/G	0.388	0.95	0.90-1.01	9.32E-02	1.05	1.03-1.06	2.01E-07	0.95	0.92-0.99	7.85E-03	0.95	0.92-0.99	7.52E-03	1.04	1.01-1.06	9.26E-04	1.02	0.99-1.05	2.94E-01	1.00	0.96-1.04	9.74E-01	1.00	0.96-1.01	1.07E-01	1.04	1.01-1.08	1.11E-02
r12817822	17	757175	T/G	0.01	1.07	1.05-1.17	7.86E-04	1.13	1.10-1.21	1.17E-01	1.14	1.10-1.15	2.62E-04	1.14	1.10-1.16	5.56E-05	1.10	0.96-1.25	1.17E-01	1.12	1.06-1.13	1.41E-01	1.15	1.06-1.13	2.19E-01	1.10	0.95-1.01	4.31E-05	0.67	0.57-0.80	5.07E-06
r382483	18	1051644	G/A	0.496	0.95	0.90-1.00	6.46E-02	1.03	1.01-1.05	2.13E-04	0.98	0.95-1.01	2.91E-01	0.98	0.95-1.01	2.37E-01	1.03	1.01-1.05	5.91E-03	0.99	0.96-1.02	3.62E-01	0.99	0.95-1.02	4.52E-01	0.99	0.95-1.02	7.10E-03	0.95	0.92-0.98	4.81E-04
r131526427	20	131526427	A/CAC	0.25	0.98	0.91-1.04	4.56E-01	0.96	0.94-0.98	1.94E-06	0.94	0.90-0.99	9.54E-01	0.94	0.90-0.98	2.79E-01	0.96	0.94-0.99	1.61E-01	0.95	0.91-0.99	3.78E-01	0.95	0.91-0.99	2.66E-01	1.05	1.01-1.09	2.02E-02	1.04	1.01-1.08	1.56E-02
r9808224	20	3924826	G/A	0.393	1.01	0.95-1.07	7.40E-01	0.96	0.94-0.97	7.08E-08	0.96	0.92-0.99	1.71E-02	0.96	0.94-0.98	1.89E-05	0.98	0.95-1.01	1.21E-01	0.96	0.92-0.99	2.33E-02	0.97	0.96-1.06	8.78E-02	1.04	1.01-1.08	2.99E-02	1.04	1.01-1.07	1.19E-03
r13212131	6	3321996	C/T	0.08	1.05	0.95-1.16	2.97E-01	0.99	0.95-1.02	6.07E-01	0.97	0.91-1.04	4.80E-01	0.99	0.93-1.06	8.45E-01	0.97	0.91-1.03	8.10E-02	0.96	0.90-1.01	1.20E-01	0.94	0.8							

Supplementary Table 12: Fifteen variants identified with evidence of heterogeneity (n = 106,278 invasive cases, n = 91,477 controls).

Lead variant	CHR	Position	Marker specific heterogeneity ² case-case OR, 95% CI, and P-values												
			Global Heterogeneity Test P ¹	ER OR ³ (95%CI)	PR OR ³ (95%CI) 95%CI	HER2 OR ³ (95%CI) 95%CI	Grade OR ³ (95%CI) 95%CI								
1:145126177	1	145,126,177	2.8 x 10 ⁻⁶	0.97	0.87-1.07	5.0 x 10 ⁻¹	1.09	1.00-1.19	5.4 x 10 ⁻²	0.92	0.83-1.02	1.2 x 10 ⁻¹	0.92	0.87-0.96	6.9 x 10 ⁻⁴
rs9712235	2	67,881,757	6.7 x 10 ⁻³	0.94	0.90-0.97	3.7 x 10 ⁻⁴	1.04	1.01-1.07	2.4 x 10 ⁻²	0.96	0.92-1.00	2.8 x 10 ⁻²	1.00	0.98-1.02	8.5 x 10 ⁻¹
rs138044103	5	67,424,121	5.2 x 10 ⁻⁷	1.02	0.99-1.06	1.7 x 10 ⁻¹	1.02	0.99-1.05	1.3 x 10 ⁻¹	1.01	0.98-1.05	4.2 x 10 ⁻¹	0.98	0.96-0.99	2.8 x 10 ⁻³
rs17215231	6	33,239,869	2.4 x 10 ⁻⁶	1.07	1.00-1.14	4.4 x 10 ⁻²	1.03	0.98-1.09	2.5 x 10 ⁻¹	1.08	1.02-1.15	9.1 x 10 ⁻³	0.96	0.93-0.99	7.9 x 10 ⁻³
rs7760611	6	21,903,533	1.4 x 10 ⁻³	0.96	0.93-1.00	2.7 x 10 ⁻²	0.98	0.96-1.01	2.8 x 10 ⁻¹	0.98	0.95-1.01	1.7 x 10 ⁻¹	1.00	0.99-1.02	8.7 x 10 ⁻¹
rs79518236	7	98,026,554	1.6 x 10 ⁻³	0.98	0.95-1.02	3.7 x 10 ⁻¹	0.96	0.93-0.99	1.7 x 10 ⁻²	0.98	0.94-1.02	3.0 x 10 ⁻¹	0.97	0.95-0.99	1.9 x 10 ⁻³
rs4742903	9	106,856,793	2.8 x 10 ⁻³	0.98	0.95-1.02	3.4 x 10 ⁻¹	1.01	0.99-1.04	3.7 x 10 ⁻¹	0.97	0.94-1.00	5.1 x 10 ⁻²	0.98	0.96-1.00	1.1 x 10 ⁻²
rs7924772	11	120,233,626	1.4 x 10 ⁻³	0.99	0.96-1.03	6.7 x 10 ⁻¹	1.00	0.97-1.03	8.3 x 10 ⁻¹	0.92	0.89-0.95	1.4 x 10 ⁻⁶	0.99	0.97-1.00	1.0 x 10 ⁻¹
rs2464195	12	121,435,475	1.0 x 10 ⁻²	1.03	1.00-1.06	8.9 x 10 ⁻²	1.00	0.97-1.03	9.9 x 10 ⁻¹	0.99	0.95-1.02	4.1 x 10 ⁻¹	0.99	0.98-1.01	3.4 x 10 ⁻¹
rs78378222	17	7,571,752	9.1 x 10 ⁻⁸	1.42	1.23-1.65	7.0 x 10 ⁻⁶	1.01	0.89-1.14	9.0 x 10 ⁻¹	1.29	1.13-1.48	2.7 x 10 ⁻⁴	0.98	0.91-1.05	5.2 x 10 ⁻¹
rs206435	18	10,354,649	1.1 x 10 ⁻⁹	1.05	1.02-1.08	2.8 x 10 ⁻³	0.98	0.96-1.01	2.5 x 10 ⁻¹	0.98	0.95-1.01	1.4 x 10 ⁻¹	0.97	0.96-0.99	2.8 x 10 ⁻⁴
rs17743054	18	42,900,892	1.9 x 10 ⁻²	1.00	0.97-1.04	8.4 x 10 ⁻¹	0.99	0.96-1.02	5.3 x 10 ⁻¹	1.01	0.97-1.04	6.8 x 10 ⁻¹	1.02	1.00-1.04	2.6 x 10 ⁻²
rs6065254	20	39,248,265	7.3 x 10 ⁻⁷	0.95	0.92-0.98	4.3 x 10 ⁻³	0.98	0.95-1.01	2.0 x 10 ⁻¹	0.99	0.95-1.02	3.9 x 10 ⁻¹	1.01	0.99-1.03	2.7 x 10 ⁻¹
rs141526427	20	11,502,618	6.2 x 10 ⁻⁵	0.94	0.90-0.98	1.3 x 10 ⁻³	0.99	0.95-1.02	4.4 x 10 ⁻¹	0.97	0.93-1.01	8.9 x 10 ⁻²	0.99	0.97-1.01	3.2 x 10 ⁻¹
rs13039563	20	52,296,849	4.9 x 10 ⁻³	1.03	0.99-1.07	1.4 x 10 ⁻¹	1.02	0.99-1.05	2.6 x 10 ⁻¹	1.01	0.97-1.04	8.1 x 10 ⁻¹	0.99	0.97-1.01	4.4 x 10 ⁻¹

¹ Global heterogeneity tests were evaluated using a mixed effect two-stage polytomous model adjusted for top 10 PCs and age while accounting subtypes heterogeneity for ER (fixed effect), PR (random effect), HER2(random

² The marker specific heterogeneity test was evaluated using a fixed effect two-stage polytomous model adjusted for top 10 PCs and age while accounting subtypes heterogeneity for ER, PR, HER2 and grade all as fixed effect

³ Case-case per minor-allele odds ratios were estimated with fixed-effect two-stage polytomous models, mutually adjusting for each tumor marker

⁴ P-values are raw p-values from two-tailed z-test statistics.

effect), and grade (random effect). The global heterogeneity test was corrected for multiple testing using a False Discovery Rate (FDR) of 0.05 under the Benjamini-Hochberg procedure

:s

Supplementary Table 7: Three novel variants identified as being associated with risk of triple negative breast cancer using meta-analysis of BCAC and CIMBA data (BCAC: n = 8,602 effective triple-negative cases, n = 91,477 controls; CIMBA: n = 1,000 effective triple-negative cases, n = 1,000 controls)

Lead variant	Chr. ¹	Position	Alleles ²	MAF ³	Imputation Quality	BCAC triple negative			CIMBA BRCA1 mutation carriers			Meta-analysis		
						iCOGS/ONCO ⁴	OR ⁵	95% CI	P ⁶	HR ⁷	95%CI	P ⁶	RR ⁸	95%CI
rs17215231	6	33,239,869	C/T	0.08	0.82/1.00	0.82	0.77-0.87	2.2 x 10 ⁻¹⁰	0.88	0.82-0.94	2.7 x 10 ⁻⁴	0.85	0.81-0.89	8.6 x 10 ⁻¹³
rs2464195	12	121,435,475	G/A	0.37	1.00/1.00	0.94	0.91-0.97	5.3 x 10 ⁻⁵	0.93	0.90-0.96	1.1 x 10 ⁻⁴	0.93	0.91-0.96	2.5 x 10 ⁻⁸
rs78378222 ⁸	17	7,571,752	T/G	0.01	0.90/1.00	0.67	0.56-0.79	4.8 x 10 ⁻⁶	0.71	0.58-0.86	7.2 x 10 ⁻⁴	0.69	0.62-0.77	1.4 x 10 ⁻⁸

¹ Chr., chromosome

² Major alleles listed first

³ MAF, minor allele frequency

⁴ Imputation quality (r^2) for iCOGS/OncoArray

⁵ OR, per minor-allele odds ratio estimated using the fixed-effects two-stage model

⁶ P-values are raw p-values from two-tailed z-test statistics. Bonferroni correction was used to account for multiple testing (cut off P-value = 5x 10⁻⁸).

⁷ HR, per minor-allele hazard ratio

⁸ RR, per minor-allele relative risk was estimated through fixed effect meta-analysis of BCAC and CIMBA data

⁹ rs78378222 was detected in both the two-stage model and the meta-analysis of BCAC triple negative and CIMBA-BRCA1 mutation carriers

BA BRCA1 carriers: n = 9,414 cases, n = 9,494 controls).

Supplementary Table 8: Conditional analysis of genome-wide significant variants from standard logistic regression analyses of overall breast cancer risk conditional on near

Lead variant ¹	Chr. ²	Position	MAF ³	Nearby known variant ⁴	LD ⁵	D' ⁶	Standard analysis P ⁷	Conditional analysis P ⁸
rs150157076	1	120,586,681	0.47	rs11249433	0.03	0.17	1.0 x 10 ⁻¹⁰	2.4 x 10 ⁻³
rs11264454	1	156,153,043	0.43	rs4971059	0.02	0.27	1.7 x 10 ⁻⁸	1.1 x 10 ⁻⁵
rs11749176	5	44,145,931	0.14	rs10941679	0.03	0.75	8.6 x 10 ⁻¹⁰	1.1 x 10 ⁻²
5:45333860	5	45,333,860	0.24	rs10941679	0.06	0.72	3.9 x 10 ⁻²¹	6.8 x 10 ⁻⁵
rs141930488	5	51,248,274	0.02	rs35951924	0.06	0.72	3.5 x 10 ⁻⁸	1.8 x 10 ⁻⁶
rs6860806	5	131,640,536	0.46	rs6596100	0	0.04	2.7 x 10 ⁻⁸	1.5 x 10 ⁻⁶
rs7760611⁹	6	21,903,533	0.47	rs2223621	0	0.01	1.5 x 10⁻⁹	4.5 x 10⁻⁹
rs13277568⁹	8	116,679,547	0.37	rs13267382	0	0.01	2.2 x 10⁻⁸	3.1 x 10⁻⁷
rs12765365	10	64,848,937	0.04	rs10995201	0.05	0.46	9.1 x 10 ⁻⁹	1.1 x 10 ⁻²
12:29140260⁹	12	29,140,260	0.09	rs7297051	0	0.02	7.7 x 10⁻¹²	8.2 x 10⁻¹¹
rs1061657⁹	12	115,108,136	0.26	rs1292011	0	0	2.5 x 10⁻¹⁰	1.4 x 10⁻¹¹
rs17743054⁹	18	42,900,892	0.28	rs6507583	0	0.11	1.5 x 10⁻¹⁰	1.4 x 10⁻¹⁰

¹ Showing the strongest signal in each region

² Chr., chromosome

³ MAF, minor allele frequency

⁴ Known variantss previous published in Michailidou et al. Nature 551, no. 7678 (2017) and Milne et al. Nat Genet 49, 1767-1778 (2017)

⁵ LD, linkage disequilibrium between lead variant and nearby known variant estimated from European-ancestry controls in OncoArray

⁶ D', D prime between lead variant and nearby known variant estimated from European-ancestry controls in OncoArray

⁷ Standard logistic regression p-value

⁸ Standard logistic regression p-value adjusting for nearby known variant, a conditional significance p-value threshold of $P < 1 \times 10^{-6}$ was used (reason described in **Online Methor**

⁹ Conditionally significant after adjusting for nearby known variant

ry (within +/- 2 MB) known breast cancer loci (n = 133,384 cases, n = 113,789 controls).

is)

Supplementary Table 9: Results from conditional analyses of genome-wide significant variants identified by two-stage regression models that are located nearby (within +/- 2 MB) a known

Lead variant ¹	Chr. ²	Position	MAF ³	Nearby known variant ⁴	LD ⁵	D' ⁶	Mixed effect model global association test P ⁷	Conditional analysis P ⁸
rs6697258	1	120,485,335	0.06	rs11249433	0.06	0.68	1.5 x 10 ⁻¹⁵	3.2 x 10 ⁻³
1:145126177⁹	1	145,126,177	0.04	rs12405132	0.03	0.4	9.6 x 10⁻⁹	6.8 x 10⁻¹⁰
rs6677545	1	200,342,046	0.35	rs35383942 rs6678914	0 0.01	0.01 0.05	4.3 x 10 ⁻⁸	1.3 x 10 ⁻⁶
rs56826596	5	45,374,890	0.15	rs10941679	0.09	0.41	7.8 x 10 ⁻¹²	1.7 x 10 ⁻¹
rs139331653	5	45,939,294	0.03	rs10941679	0.07	0.92	2.4 x 10 ⁻⁹	2.7 x 10 ⁻¹
rs34044188	10	65,257,363	0.05	rs10995201	0.04	0.43	8.7 x 10 ⁻⁹	5.0 x 10 ⁻³
rs16988381	22	30,592,808	0.02	rs17879961 rs132390	0.02 0	0.3 0.01	2.8 x 10 ⁻⁹	1.2 x 10 ⁻⁶

¹ Showing the strongest signal in each region

² Chr., chromosome

³ MAF, minor allele frequency

⁴ Known variants previously published in Michailidou et al. Nature 551, no. 7678 (2017) and Milne et al. Nat Genet 49, 1767-1778 (2017)

⁵ LD, linkage disequilibrium between lead variant and nearby known variant estimated from European-ancestry controls in OncoArray

⁶ D', D prime between lead variant and nearby known variant estimated from European-ancestry controls in OncoArray

⁷ Results from mixed effect two-stage models adjusting for estrogen receptor (ER, fixed effect), progesterone receptor (PR, random effect), human epidermal growth factor receptor 2 (HER2, ra

⁸ Results from mixed effect two-stage models global association test conditional on the nearby known variants, p-value threshold of $p < 1 \times 10^{-6}$ was used for conditional analyses (reason descri

⁹ Conditionally significant after adjusting for nearby known variant

breast cancer susceptibility variant (n = 106,278 invasive cases, n = 91,477 controls).

andom effect), and grade (random effect)
bed in **Online Methods**)

Supplementary Table 13: Enhancer states of candidates causal variants (CCVs) for the 32 identified variants

Analysis ¹	Lead variant ²	Variant Name ³	Number of CCVs ⁴	Number of CCVs enhancers ⁵	OFF.PRIMED ⁶	ACTIVE.PRIMED ⁷	ACTIVE.OFF ⁸	ACTIVE.OFF.PRIMED ⁹	CCVs in ANYSWITCH enhancers ¹⁰	Opposite direction variant ¹¹
Overall analysis	rs5776993	1_110222901_CA_C	7	3	1	0	0	1	Y	N
Overall analysis	rs10838267	11_44368892_G_A	14	11	1	0	1	0	Y	N
Overall analysis	rs11065822	12_111600134_G_T	18	3	1	1	1	0	Y	N
Overall analysis	rs1061657	12_115108136_T_C	6	0	0	0	0	0	N	N
Overall analysis	12:29140260	12_29140260_G_A	41	0	0	0	0	0	N	N
Overall analysis	rs11652463	17_70405095_C_G	3	2	0	0	1	0	Y	N
Overall analysis	rs12962334	18_20477934_G_C	128	8	1	0	1	0	Y	N
Overall analysis	rs17743054	18_42900892_T_C	26	0	0	0	0	0	N	N
Overall analysis	rs9712235	2_67881757_G_A	18	3	1	0	0	0	Y	N
Overall analysis	rs4602255	2_69392128_G_A	27	9	1	0	1	1	Y	N
Overall analysis	rs13039563	20_52296849_G_A	11	3	1	0	0	0	Y	N
Overall analysis	rs9808759	21_47780223_T_C	38	5	1	0	1	0	Y	N
Overall analysis	rs34052812	3_156535958_AT_A	82	1	0	0	1	0	Y	N
Overall analysis	rs1375631	3_16778867_A_G	13	0	0	0	0	0	N	N
Overall analysis	rs2886671	3_59373745_C_T	30	0	0	0	0	0	N	N
Overall analysis	rs7760611	6_21903533_T_C	15	1	1	0	0	0	Y	N
Overall analysis	rs188092014	7_74341926_G_C	56	4	0	0	0	0	N	N
Overall analysis	rs79518236	7_98026554_ACT_A	45	10	1	1	1	0	Y	N
Overall analysis	rs13277568	8_116679547_A_G	3	0	0	0	0	0	N	N
Overall analysis	rs142890050	8_23480253_CTT_C	41	4	1	0	0	0	Y	N
Overall analysis	rs13256025	8_25831778_C_T	1	1	0	0	0	0	N	N
Overall analysis	rs4742903	9_106856793_G_C	102	0	0	0	0	0	N	N
Subtypes analysis	1:145126177	1_145126177_G_A	28	2	1	1	0	0	Y	N
Subtypes analysis	rs7924772	11_120233626_A_G	93	9	1	1	1	0	Y	Y
Subtypes analysis	rs78378222	17_7571752_T_G	2	1	0	0	0	1	Y	Y
Subtypes analysis	rs206435	18_10354649_A_C	50	11	1	0	0	0	Y	Y
Subtypes analysis	rs141526427	20_11502618_A_AAC	5	1	0	0	1	0	Y	Y
Subtypes analysis	rs6065254	20_39248265_G_A	27	5	1	0	0	1	Y	Y
Subtypes analysis	rs495367	4_1986972_A_G	2	1	0	0	1	0	Y	N
Subtypes analysis	rs138044103	5_67424121_C_C TG	110	3	0	0	1	0	Y	N
TN analysis	rs17215231	12_121435475_G_A	67	16	1	0	1	1	Y	N
TN analysis	rs2464195	6_33239869_C_T	2	0	0	0	0	0	N	N

¹ Results from three different analysis; the overall analysis using standard logistic regression (overall analysis), the subtypes analysis using two-stage polytomous model (subtypes analysis), and the meta-analysis between BCAC TN and CIMBAB.

² The most significant variants identified in the three different analysis

³ The variant name coded as chromosome_position_reference allele_effect allele

⁴ Number of CCVs within 500kb of the lead variant and with P values within 100-fold of magnitude of the most significant variants

⁵ Number of CCVs overlapping enhancers

⁶ Indicator of enhancer states in three normal breast epithelial sub-populations. If any enhancer is "OFF" in one sub-population and "PRIMED" in another sub-population, then it's coded as 1, otherwise as 0

⁷ Indicator of enhancer states in three normal breast epithelial sub-populations. If any enhancer is "ACTIVE" in one sub-population and "PRIMED" in another sub-population, then it's coded as 1, otherwise as 0

⁸ Indicator of enhancer states in three normal breast epithelial sub-populations. If any enhancer is "ACTIVE" in one sub-population and "OFF" in another sub-population, then it's coded as 1, otherwise as 0

⁹ Indicator of enhancer states in three normal breast epithelial sub-populations. If any enhancer is "ACTIVE" in one sub-population, "OFF" in another sub-population and "PRIMED" in the third sub-population, then it's coded as 1, otherwise as 0

¹⁰ Indicator of "ANYSWITCH" enhancers. "ANYSWITCH" enhancers exhibit different states between cell types. If there is any CCV in a "ANYSWITCH" enhancer, then it's coded as Y, otherwise as N

¹¹ Indicator of variants with opposite associations in different breast intrinsic-like subtypes

RCA1 carriers (TN analysis)

TN analysis	rs17215231	12_121435475_G_A	12_121416988_A_G	1	0	0	1	0	0	0	0	1
TN analysis	rs17215231	12_121435475_G_A	12_121417536_G_GACTC	1	0	0	0	0	0	0	0	1
TN analysis	rs17215231	12_121435475_G_A	12_121419926_T_C	1	0	0	1	0	0	0	0	1
TN analysis	rs17215231	12_121435475_G_A	12_121420260_A_G	1	0	0	1	0	0	0	0	1
TN analysis	rs17215231	12_121435475_G_A	12_121420263_A_G	1	0	0	1	0	0	0	0	1
TN analysis	rs17215231	12_121435475_G_A	12_121422449_CTAGCTGGCACTCAGCA_T	1	0	0	1	0	0	0	1	0
TN analysis	rs17215231	12_121435475_G_A	12_121423285_T_C	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121423376_G_A	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121423386_A_G	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121423659_A_G	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121423956_C_T	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121424406_G_A	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121424490_C_T	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121424574_G_A	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121426064_C_T	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121426478_C_T	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121426594_G_A	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121428407_A_G	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121431300_C_T	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121432603_C_T	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121434833_G_A	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121435342_C_T	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121435427_G_A	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121435475_G_A	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121438311_C_T	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121438844_T_C	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121439192_G_T	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121439433_G_A	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121440731_C_T	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121441461_G_T	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121443116_A_G	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121443753_T_G	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121444441_CAT_C	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121445808_T_C	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121446446_T_A	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121450165_C_T	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121450354_C_A	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121450384_G_C	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121452249_C_T	1	0	0	1	0	0	0	1	0
TN analysis	rs17215231	12_121435475_G_A	12_121454313_C_A	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121454906_G_A	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121455873_C_T	0	0	0	0	0	0	0	0	0
TN analysis	rs17215231	12_121435475_G_A	12_121477359_G_T	1	0	0	0	0	1	0	0	0
TN analysis	rs2464195	6_33239869_C_T	12_121489586_ATT_A	0	0	0	0	0	0	0	0	0
TN analysis	rs2464195	6_33239869_C_T	6_33239869_C_T	0	0	0	0	0	0	0	0	0
TN analysis	rs2464195	6_33239869_C_T	6_33239869_G_A	0	0	0	0	0	0	0	0	0

¹ Results from three different analysis: the overall analysis using standard logistic regression (overall analysis), the subtypes analysis using two-stage polytomous model (subtypes analysis), and the meta-analysis between BCAC TN and CIMBABRCA1 carriers (TN analysis)

² The most significant variants identified in the three different analysis

³ The variant name coded as chromosome_position_reference_allele_effect allele

⁴ Number of candidates causal variants (CCVs) within 500kb of the lead variant and with P values within 100-fold of magnitude of the most significant variants

⁵ Indicator of "OFF" enhancer in basal cell. If this CCV overlaps with an "OFF" enhancer in basal cell, then it's coded as 1, otherwise as 0

⁶ Indicator of "PRIMED" enhancer in basal cell. If this CCV overlaps with an "PRIMED" enhancer in basal cell, then it's coded as 1, otherwise as 0

⁷ Indicator of "ACTIVE" enhancer in basal cell. If this CCV overlaps with an "ACTIVE" enhancer in basal cell, then it's coded as 1, otherwise as 0

⁸ Indicator of "OFF" enhancer in basal cell. If this CCV overlaps with an "OFF" enhancer in basal cell, then it's coded as 1, otherwise as 0

⁹ Indicator of "PRIMED" enhancer in luminal progenitor cell. If this CCV overlaps with an "PRIMED" enhancer in luminal progenitor cell, then it's coded as 1, otherwise as 0

¹⁰ Indicator of "ACTIVE" enhancer in luminal progenitor cell. If this CCV overlaps with an "ACTIVE" enhancer in luminal progenitor cell, then it's coded as 1, otherwise as 0

¹¹ Indicator of "OFF" enhancer in mature luminal cell. If this CCV overlaps with an "OFF" enhancer in mature luminal cell, then it's coded as 1, otherwise as 0

¹² Indicator of "PRIMED" enhancer in mature luminal cell. If this CCV overlaps with an "PRIMED" enhancer in mature luminal cell, then it's coded as 1, otherwise as 0

¹³ Indicator of "ACTIVE" enhancer in mature luminal cell. If this CCV overlaps with an "ACTIVE" enhancer in mature luminal cell, then it's coded as 1, otherwise as 0

Supplementary Table 15: INQUISIT analysis results

Analysis ¹	Region ²	Target gene ³	INQUIST category ⁴	FINAL INQUISIT SCORE LEVEL ⁵
Overall analysis	12_111600134_G_T	ATXN2	DISTAL	1
Overall analysis	12_115108136_T_C	TBX3	DISTAL	1
Overall analysis	18_20477934_G_C	RBBP8	DISTAL	1
Overall analysis	20_52296849_G_A	ZNF217	DISTAL	1
Overall analysis	21_47780223_T_C	C21orf58	DISTAL	1
Overall analysis	21_47780223_T_C	DIP2A	DISTAL	1
Overall analysis	21_47780223_T_C	PCNT	DISTAL	1
Overall analysis	21_47780223_T_C	YBEY	DISTAL	1
Overall analysis	3_156535958_AT_A	LEKR1	DISTAL	1
Overall analysis	3_156535958_AT_A	LINC00886	DISTAL	1
Overall analysis	3_156535958_AT_A	TIPARP	DISTAL	1
Overall analysis	3_156535958_AT_A	TIPARP-AS1	DISTAL	1
Overall analysis	6_21903533_T_C	SOX4	DISTAL	1
Overall analysis	7_74341926_G_C	GTF2I	DISTAL	1
Overall analysis	7_98026554_ACT_A	BAIAP2L1	DISTAL	1
Overall analysis	7_98026554_ACT_A	BRI3	DISTAL	1
Subtypes analysis	1_145126177_G_A	PDE4DIP	DISTAL	1
Subtypes analysis	1_145126177_G_A	TXNIP	DISTAL	1
Subtypes analysis	11_120233626_A_G	ARHGEF12	DISTAL	1
Subtypes analysis	11_120233626_A_G	TMEM136	DISTAL	1
Subtypes analysis	20_39248265_G_A	MAFB	DISTAL	1
Subtypes analysis	4_1986972_A_G	C4orf48	DISTAL	1
TN analysis	12_121435475_G_A	C12orf43	PROMOTER	1
Overall analysis	1_110222901_CA_C	AMPD2	DISTAL	2
Overall analysis	1_110222901_CA_C	GNAI3	DISTAL	2
Overall analysis	1_110222901_CA_C	GSTM3	DISTAL	2
Overall analysis	1_110222901_CA_C	GSTM4	DISTAL	2
Overall analysis	1_110222901_CA_C	RP5-1160K1.8	DISTAL	2
Overall analysis	1_110222901_CA_C	GSTM1	PROMOTER	2
Overall analysis	12_111600134_G_T	CUX2	DISTAL	2
Overall analysis	12_111600134_G_T	RP11-686G8.2	DISTAL	2
Overall analysis	12_111600134_G_T	SH2B3	DISTAL	2
Overall analysis	12_115108136_T_C	TBX3	DISTAL	2

Supplementary Table 16: Genetic correlation between the five intrinsic-like breast cancer subtypes¹ and CIMBA *BRCA1* carriers estimated by LD-score regression²

Genetic correlation (SE)	Luminal A-like	Luminal B/HER2-negative-like	Luminal B-like	HER2-enriched-like	TN	CIMBA <i>BRCA1</i>
Luminal A-like	1 (0)					
Luminal B/HER2-negative-like	0.80 (0.05)	1 (0)				
Luminal B-like	0.74 (0.05)	0.69 (0.07)	1 (0)			
HER2-enriched-like	0.57 (0.07)	0.59 (0.11)	0.35 (0.10)	1 (0)		
TN	0.46 (0.05)	0.40 (0.08)	0.60 (0.08)	0.56 (0.13)	1 (0)	
CIMBA <i>BRCA1</i>	0.39 (0.09)	0.31 (0.12)	0.38 (0.16)	0.80 (0.24)	0.84 (0.15)	1 (0)

¹ 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-e

² LD-score regression was described in Nat Genet 47, 291-5 (2015). and Nat Genet 47, 1236-41 (2015)

enriched-like (ER- and PR-, HER2+), and triple-negative (ER-, PR-, HER2-)

Supplementary table 17: Enrichment analysis based on 53 genomic features (n = 45,253 effective luminal A-like cases, n = 8,602 effective triple-nega

Annotation ¹	Proportion variants	Proportion heritability	Enrichment	P-value
HR+, HER2-, low grade				
H3K27ac ² , extend500bp	0.42	0.93	2.19	2.5 x 10 ⁻¹⁴
H3K27ac ²	0.39	0.85	2.17	7.6 x 10 ⁻¹³
Super-enhancers, extend500bp	0.17	0.5	2.93	1.3 x 10 ⁻¹²
Super-enhancers	0.17	0.48	2.87	1.7 x 10 ⁻¹¹
H3K27ac ³ , extend500bp	0.34	0.85	2.54	1.0 x 10 ⁻⁹
H3K4me1	0.43	1.03	2.41	4.6 x 10 ⁻⁸
Repressed, extend500bp	0.72	0.42	0.58	8.1 x 10 ⁻⁸
TFBS, extend500bp	0.34	0.91	2.66	1.1 x 10 ⁻⁶
Digital genomic footprint, extend500bp	0.54	1.07	1.98	1.6 x 10 ⁻⁶
H3K4me1, extend500bp	0.61	0.93	1.53	4.5 x 10 ⁻⁵
H3K4me3	0.13	0.6	4.53	4.8 x 10 ⁻⁵
H3K4me3, extend500bp	0.26	0.63	2.47	9.7 x 10 ⁻⁵
H3K3me peaks	0.17	0.85	4.98	1.2 x 10 ⁻⁴
Transcription factor binding site	0.13	0.72	5.47	1.5 x 10 ⁻⁴
Conserved	0.33	0.75	2.25	1.8 x 10 ⁻⁴
H3K9ac	0.23	0.6	2.62	2.1 x 10 ⁻⁴
Triple Negative				
Super-enhancers, extend500bp	0.17	0.52	3.04	3.3 x 10 ⁻⁶
H3K27ac ² , extend500bp	0.42	0.87	2.05	5.2 x 10 ⁻⁵
Super-enhancers	0.17	0.49	2.91	1.2 x 10 ⁻⁴
Digital genomic footprint, extend500bp	0.54	1.18	2.19	4.0 x 10 ⁻⁴
H3K27ac ²	0.39	0.82	2.09	4.5 x 10 ⁻⁴

¹ Of the 52 baseline genomic features described in Finucane, H.K. et al. Partitioning heritability by functional annotation using genome-wide association

² Hnisz, D. et al. Super-enhancers in the control of cell identity and disease. *Cell* 155, 934-47 (2013)

³ Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511,

Supplementary Table 18: Comparison of genetic variance estimates of invasive breast cancer subtypes between two-stage polytomous model with missing data algorithm¹ and st

Phenotype	Genetic variance for all GWAS variants	The variance of genetic variance estimate for all GWAS variants ⁴
Luminal A-like	0.620	0.056
Luminal A-like complete data only	0.592	0.063
Luminal B/HER2-negative-like	0.740	0.093
Luminal B/HER2-negative-like complete data only	0.751	0.093
Luminal B-like	0.597	0.077
Luminal B-like complete data only	0.563	0.098
HER2-enriched-like	0.689	0.154
HER2-enriched-like complete data only	0.612	0.187
Triple negative	0.492	0.072
Triple negative complete data only	0.520	0.085

¹ Two-stage polytomous model was fitted for the five intrinsic-like subtypes using a missing data algorithm

² Standard polytomous model was fitted for the five intrinsic-like subtypes using on the complete data

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)

⁴ The variance of the genetic variance estimate of all reliably genome-wide imputable variants was estimated through LD-score regression described in Nat Genet 47, 291-5 (2015). and

Standard polytomous model restricting to complete data²

i).

Nat Genet 47, 1236-41 (2015).

Supplementary Table 19: Effect sizes for 330 SNPs used to construct the intrinsic subtypes-like polygenic risk score (PRS)

Var name ¹	variant ²	CHR	Position	Reference allele	Effect allele	EAF ³	Log odds ratio of effect allele for intrinsic-like subtypes				
							Luminal A-like	Luminal B/HER2-negative-like	Luminal B-like	HER2-enriched-like	TN
1_100880328_A_T	rs612683	1	100880328	A	T	0.41	0.04	0.03	0.02	-0.02	0.03
1_10566215_A_G	rs616488	1	10566215	A	G	0.32	-0.03	-0.05	-0.12	-0.18	-0.08
1_110198129_CAAA_C	rs56097627	1	110198129	CAAA	C	0.78	0.05	0.07	0.03	0.06	0.04
1_114445880_G_A	rs7513707	1	114445880	G	A	0.17	0.06	0.04	0.05	0.05	0.06
1_118141492_A_C	rs12406858	1	118141492	A	C	0.27	0.03	0.05	0.01	0.03	0.02
1_120257110_T_C	rs637868	1	120257110	T	C	0.53	0.04	0.03	0.03	0.01	0.01
1_121280613_A_G	rs11249433	1	121280613	A	G	0.42	0.15	0.06	0.06	-0.02	0.02
1_121287994_A_G	rs111458676	1	121287994	A	G	0.10	-0.17	-0.05	-0.05	-0.05	0.01
1_145604302_C_CT	rs72127681	1	145604302	C	CT	0.34	-0.05	-0.07	-0.07	-0.01	-0.01
1_149906413_T_C	rs11205303	1	149906413	T	C	0.41	0.07	0.02	0.05	0.01	0.04
1_155556971_G_A	rs12091730	1	155556971	G	A	0.23	0.06	0.05	0.04	0.08	0.00
1_168171052_CA_C	rs139315904	1	168171052	CA	C	0.11	-0.07	-0.05	-0.10	-0.04	-0.09
1_172328767_T_TA	rs11463354	1	172328767	T	TA	0.33	-0.03	-0.01	-0.06	-0.10	-0.06
1_18807339_T_C	rs2992756	1	18807339	T	C	0.51	-0.06	-0.07	-0.08	-0.02	-0.02
1_201437832_C_T	rs35383942	1	201437832	C	T	0.06	0.11	0.02	0.16	0.15	0.08
1_202184600_C_T	rs6686987	1	202184600	C	T	0.40	0.02	0.00	0.00	-0.15	-0.06
1_203770448_T_A	rs7514172	1	203770448	T	A	0.28	0.06	0.02	0.07	0.08	0.04
1_204502514_T_TTCTGAAACAGGG	rs11268668	1	204502514	T	TTCTGAAACAGGG	0.80	0.02	-0.07	-0.03	-0.08	-0.18
1_208076291_G_A	rs208076291	1	208076291	G	A	0.33	-0.03	-0.09	-0.04	-0.03	-0.04
1_217053815_T_G	rs2576261	1	217053815	T	G	0.33	0.03	0.03	0.05	0.06	0.03
1_217220574_G_A	rs11117758	1	217220574	G	A	0.21	-0.06	-0.04	-0.06	0.00	-0.01
1_220671050_C_T	rs11118563	1	220671050	C	T	0.25	0.03	0.07	0.02	0.04	0.01
1_242034263_A_G	rs72755295	1	242034263	A	G	0.03	0.15	0.14	0.17	0.12	0.12
1_41380440_C_T	rs4233486	1	41380440	C	T	0.65	0.05	0.03	0.04	0.10	0.02
1_41389220_T_C	rs114282204	1	41389220	T	C	0.02	0.12	0.12	0.09	0.22	0.12
1_46670206_TC_T	rs144105764	1	46670206	TC	T	0.30	0.05	0.04	0.00	0.06	0.00
1_51467096_CT_C	rs56168262	1	51467096	CT	C	0.49	0.03	0.06	0.05	0.03	0.01
1_7917076_G_A	rs707475	1	7917076	G	A	0.38	-0.03	-0.02	-0.03	-0.04	-0.05
1_88156923_G_A	rs17426269	1	88156923	G	A	0.15	0.06	0.04	0.00	0.00	0.03
1_88428199_C_A	rs2151842	1	88428199	C	A	0.24	-0.04	-0.02	-0.06	-0.05	-0.03
2_10138983_T_C	rs78425380	2	10138983	T	C	0.12	0.07	0.03	0.11	0.09	0.01
2_121058254_A_G	rs6746250	2	121058254	A	G	0.70	-0.02	-0.03	0.00	-0.05	-0.08
2_121089731_T_C	rs17625845	2	121089731	T	C	0.19	-0.02	-0.04	-0.06	-0.06	-0.12
2_121159205_G_A	rs10164550	2	121159205	G	A	0.35	-0.06	-0.02	-0.01	-0.01	-0.03
2_121246568_T_C	rs10179592	2	121246568	T	C	0.90	0.09	0.13	0.12	0.10	0.14
2_172974566_C_G	rs17726078	2	172974566	C	G	0.47	-0.08	-0.01	-0.03	-0.04	0.01
2_174212910_A_G	rs1550622	2	174212910	A	G	0.85	0.05	0.08	0.14	0.08	0.00
2_192381934_C_T	rs2356656	2	192381934	C	T	0.86	0.01	-0.01	0.03	0.10	0.08
2_19315675_T_A	rs6743383	2	19315675	T	A	0.55	-0.03	-0.05	-0.02	-0.04	-0.08
2_202204741_T_C	rs10197246	2	202204741	T	C	0.71	-0.04	-0.04	-0.06	-0.02	-0.07
2_217920769_G_T	rs4442975	2	217920769	G	T	0.48	-0.18	-0.11	-0.11	-0.10	-0.04
2_217955896_GA_G	2:217955896	2	217955896	GA	G	0.03	-0.30	-0.12	-0.13	-0.11	0.02
2_218292158_C_G	rs11693806	2	218292158	C	G	0.72	-0.08	-0.08	-0.06	-0.10	-0.05
2_218714845_G_A	rs3791977	2	218714845	G	A	0.39	-0.05	-0.03	0.00	0.03	-0.02
2_241388857_C_A	rs4676356	2	241388857	C	A	0.98	-0.10	-0.06	-0.18	-0.13	-0.15
2_25129473_A_G	rs6725517	2	25129473	A	G	0.40	-0.04	0.00	-0.08	-0.08	-0.06
2_29179452_G_C	rs12472404	2	29179452	G	C	0.23	0.03	-0.01	0.03	-0.05	-0.11
2_29615233_T_C	rs4322799	2	29615233	T	C	0.26	-0.02	-0.06	-0.05	-0.08	0.00
2_39699510_C_CT	rs11406722	2	39699510	C	CT	0.46	-0.03	-0.06	0.00	-0.02	-0.05
2_70172587_G_A	rs6756513	2	70172587	G	A	0.27	-0.04	-0.07	-0.02	0.00	-0.03
2_88358825_G_C	rs1036759	2	88358825	G	C	0.31	0.03	0.03	0.03	0.07	0.05
3_141112859_CTT_C	rs34207738	3	141112859	CTT	C	0.42	0.05	0.07	0.06	0.12	-0.01
3_172285237_G_A	rs58058861	3	172285237	G	A	0.22	0.07	0.00	0.05	0.00	-0.02
3_189774456_C_T	rs9882792	3	189774456	C	T	0.22	-0.04	-0.02	-0.02	-0.06	-0.02

3_27353716_C_A	rs552647	3	27353716	C	A	0.54	0.12	0.10	0.08	0.03	0.06
3_27388664_C_G	3:27388664	3	27388664	C	G	0.29	0.11	0.09	0.08	0.02	0.07
3_29294845_C_T	rs112476261	3	29294845	C	T	0.02	-0.12	-0.11	-0.13	-0.52	-0.24
3_30684907_C_T	rs17838698	3	30684907	C	T	0.30	0.08	0.00	0.04	-0.02	0.04
3_46888198_T_C	rs56387622	3	46888198	T	C	0.10	-0.09	-0.04	-0.13	-0.10	-0.10
3_4742251_A_G	rs6762558	3	4742251	A	G	0.39	0.07	0.06	0.06	0.09	0.03
3_49709912_C_C_T	3:49709912	3	49709912	C	CT	0.28	-0.02	-0.03	0.00	-0.06	-0.07
3_55970777_A_AT	rs138866686	3	55970777	A	AT	0.03	-0.11	-0.13	-0.11	0.07	-0.05
3_59373745_C_T	rs2886671	3	59373745	C	T	0.42	-0.04	-0.04	0.01	-0.05	-0.04
3_63887449_T_TTG	rs147250346	3	63887449	T	TTG	0.13	0.07	0.08	0.06	0.09	0.04
3_71620370_T_G	rs9825432	3	71620370	T	G	0.63	-0.03	-0.05	-0.04	-0.02	-0.06
3_87037543_A_G	rs13066793	3	87037543	A	G	0.09	-0.08	-0.11	-0.11	-0.03	-0.06
3_99403877_G_A	rs639355	3	99403877	G	A	0.48	-0.04	-0.02	-0.02	0.02	-0.03
4_106069013_G_T	rs62331150	4	106069013	G	T	0.23	0.05	0.05	0.05	-0.06	0.03
4_126752992_A_AAT	rs147399132	4	126752992	A	AAT	0.51	-0.03	-0.03	-0.04	-0.05	-0.05
4_143467195_C_T	rs56039025	4	143467195	C	T	0.11	-0.05	-0.06	-0.04	-0.03	-0.07
4_151218296_CATATTT_C	rs138786872	4	151218296	CATATTT	C	0.66	0.04	0.01	0.03	0.07	0.05
4_175842495_G_A	rs28436676	4	175842495	G	A	0.11	-0.13	-0.12	-0.12	0.00	0.04
4_175847436_C_A	rs62334414	4	175847436	C	A	0.35	0.07	0.03	0.08	0.00	-0.03
4_187503758_A_T	rs13147907	4	187503758	A	T	0.45	0.04	0.05	0.05	0.01	0.03
4_38784633_G_T	rs10012017	4	38784633	G	T	0.25	0.05	0.03	0.03	0.01	0.05
4_84370124_TAA_TA	4:84370124	4	84370124	TAA	TA	0.53	-0.04	-0.05	-0.10	-0.07	-0.04
4_89240476_G_A	rs17014016	4	89240476	G	A	0.44	0.03	0.05	0.03	0.08	0.02
4_92594859_TTCTTTC_T	rs147404208	4	92594859	TTCTTTC	T	0.44	-0.04	-0.04	-0.01	-0.08	-0.01
5_104300273_G_T	rs17157372	5	104300273	G	T	0.18	-0.04	-0.04	-0.03	0.01	-0.03
5_122478676_C_A	rs335160	5	122478676	C	A	0.74	-0.03	-0.05	-0.01	-0.03	-0.05
5_122705244_C_T	rs1428387	5	122705244	C	T	0.03	0.11	0.11	0.09	-0.04	0.08
5_1279790_C_T	rs10069690	5	1279790	C	T	0.26	0.04	0.05	0.02	0.02	0.23
5_1296255_A_AG	rs3215401	5	1296255	A	AG	0.30	-0.06	-0.06	0.00	-0.13	-0.14
5_131640536_A_G	rs6860806	5	131640536	A	G	0.55	0.04	0.05	0.05	-0.01	-0.01
5_132407058_C_T	rs6596100	5	132407058	C	T	0.24	-0.06	-0.05	-0.04	0.00	-0.01
5_1353077_T_C	rs62329727	5	1353077	T	C	0.01	0.18	0.09	0.12	0.33	0.07
5_158244083_C_T	rs1432679	5	158244083	C	T	0.56	-0.08	-0.03	-0.07	-0.03	-0.07
5_16231194_G_C	rs17611291	5	16231194	G	C	0.55	-0.05	-0.04	-0.07	-0.01	-0.05
5_169591460_T_C	rs10074269	5	169591460	T	C	0.34	0.04	0.07	0.05	-0.02	-0.01
5_173358154_G_A	rs6864691	5	173358154	G	A	0.42	0.03	0.03	0.03	0.02	0.03
5_176134882_T_C	rs4868701	5	176134882	T	C	0.54	0.04	0.01	-0.02	0.03	0.02
5_2777029_G_A	rs4866496	5	2777029	G	A	0.42	0.05	0.05	0.03	0.00	0.03
5_32579616_TCA_T	rs35130031	5	32579616	TCA	T	0.49	0.04	-0.01	0.04	0.05	-0.01
5_345109_T_C	rs116095464	5	345109	T	C	0.06	0.09	0.02	0.13	0.07	0.06
5_44508264_G_GT	rs58166936	5	44508264	G	GT	0.12	-0.10	-0.05	-0.05	-0.06	-0.03
5_44619502_A_G	rs187108781	5	44619502	A	G	0.15	-0.09	-0.07	-0.07	-0.08	-0.06
5_44649944_C_T	rs4613718	5	44649944	C	T	0.61	0.08	0.02	0.03	-0.01	-0.02
5_44706498_A_G	rs10941679	5	44706498	A	G	0.26	0.18	0.10	0.09	0.04	0.01
5_44853593_G_C	rs17343002	5	44853593	G	C	0.30	-0.07	-0.03	-0.04	-0.05	-0.01
5_52679539_C_CA	rs199562199	5	52679539	C	CA	0.10	0.05	0.05	0.06	-0.02	0.04
5_55662540_C_CT	rs113803968	5	55662540	C	CT	0.36	-0.04	-0.04	-0.04	-0.02	-0.01
5_55965167_C_T	rs889310	5	55965167	C	T	0.56	0.05	0.04	0.02	0.07	0.02
5_56023083_T_G	rs16886165	5	56023083	T	G	0.17	0.20	0.21	0.21	0.10	0.03
5_56042972_C_T	rs76250845	5	56042972	C	T	0.06	0.24	0.28	0.18	0.10	0.02
5_56045081_T_C	rs11949391	5	56045081	T	C	0.16	-0.11	-0.07	-0.07	-0.06	-0.01
5_58241712_C_T	rs113778879	5	58241712	C	T	0.57	-0.03	-0.05	-0.06	-0.07	-0.04
5_71965007_G_A	rs3010266	5	71965007	G	A	0.25	-0.05	-0.02	-0.04	-0.07	-0.01
5_73234583_T_C	rs157557	5	73234583	T	C	0.32	-0.04	-0.04	-0.05	0.02	0.00
5_77155397_GT_G	rs144028731	5	77155397	GT	G	0.34	-0.03	-0.06	-0.01	-0.03	-0.05
5_79180995_G_GA	rs34525310	5	79180995	G	GA	0.18	0.02	0.01	0.07	0.06	0.08
5_81512947_TA_T	rs146817970	5	81512947	TA	T	0.25	-0.07	-0.08	-0.02	-0.03	-0.01

5_90789470_G_A	rs332529	5	90789470	G	A	0.15	-0.09	-0.06	-0.03	0.00	-0.04
6_130341728_C_CT	rs55941023	6	130341728	C	CT	0.72	0.04	0.03	0.02	0.06	0.05
6_13713366_G_C	rs418053	6	13713366	G	C	0.56	-0.08	-0.06	-0.04	-0.04	0.01
6_149595505_T_C	rs2121348	6	149595505	T	C	0.20	-0.04	-0.08	-0.05	-0.07	0.00
6_151949806_A_C	rs6913578	6	151949806	A	C	0.32	0.06	0.08	0.11	0.18	0.16
6_151955914_A_G	rs60954078	6	151955914	A	G	0.08	0.12	0.20	0.22	0.35	0.28
6_152022664_CAAAAAAA_C	rs57589542	6	152022664	CAAAAAAA	C	0.62	0.05	0.10	0.09	0.05	0.07
6_152023191_G_A	rs851984	6	152023191	G	A	0.40	0.04	0.04	0.11	0.06	0.06
6_152055978_A_T	rs6904031	6	152055978	A	T	0.07	0.13	0.20	0.11	0.17	0.17
6_152432902_C_T	rs910416	6	152432902	C	T	0.52	0.03	0.08	0.15	0.20	0.06
6_16399557_C_T	rs3819405	6	16399557	C	T	0.33	-0.04	-0.05	-0.03	-0.05	-0.02
6_169006947_G_G	rs9364472	6	169006947	C	G	0.52	-0.02	-0.05	0.02	-0.04	-0.06
6_170332621_T_C	rs6940159	6	170332621	T	C	0.62	0.03	0.03	0.05	0.05	0.04
6_18783140_G_A	rs12211970	6	18783140	G	A	0.62	0.04	0.02	0.04	0.01	-0.03
6_20537845_CA_C	6:20537845	6	20537845	CA	C	0.47	-0.05	-0.02	-0.02	-0.02	-0.01
6_21923810_T_C	rs9358466	6	21923810	T	C	0.43	-0.05	-0.04	-0.04	-0.03	0.00
6_27425644_G_C	rs34196306	6	27425644	G	C	0.08	-0.07	-0.05	-0.08	-0.04	0.02
6_43227141_G_A	rs111342015	6	43227141	G	A	0.09	-0.05	-0.05	-0.10	-0.02	-0.05
6_82263549_AAT_A	6:82263549	6	82263549	AAT	A	0.43	0.04	0.03	0.03	0.06	0.05
6_85912194_CAA_C	rs146519950	6	85912194	CAA	C	0.06	0.06	0.03	0.03	0.08	0.07
6_87803819_T_C	rs73754909	6	87803819	T	C	0.28	0.03	0.00	0.02	0.04	0.08
7_101552440_G_A	rs71559437	7	101552440	G	A	0.12	-0.05	-0.06	-0.07	-0.01	-0.04
7_102481842_T_C	rs7800548	7	102481842	T	C	0.35	0.03	0.01	0.03	0.07	0.05
7_130656911_C_T	rs12706954	7	130656911	C	T	0.37	-0.05	-0.01	-0.02	-0.04	-0.02
7_130674481_G_A	rs68056147	7	130674481	G	A	0.30	0.06	0.04	0.04	0.02	0.05
7_139943702_CT_C	rs5887960	7	139943702	CT	C	0.55	0.07	0.07	0.05	-0.06	0.02
7_144048902_G_T	rs62485509	7	144048902	G	T	0.23	-0.05	-0.06	-0.07	-0.07	0.02
7_21940960_A_G	rs7971	7	21940960	A	G	0.35	-0.05	-0.03	-0.03	-0.02	-0.06
7_25569548_C_T	rs289997	7	25569548	C	T	0.16	-0.04	-0.02	-0.04	-0.07	-0.06
7_28869017_G_A	rs74765302	7	28869017	G	A	0.11	-0.06	-0.03	-0.08	-0.01	-0.06
7_55192256_A_C	rs13244925	7	55192256	A	C	0.54	-0.03	-0.01	-0.04	-0.01	-0.05
7_91459189_A_ATT	rs10644978	7	91459189	A	ATT	0.34	0.04	0.03	0.06	0.08	0.03
7_94113799_T_C	rs17268829	7	94113799	T	C	0.29	0.04	0.08	0.05	0.07	-0.01
7_98005235_G_A	rs4439053	7	98005235	G	A	0.16	-0.03	-0.07	-0.09	-0.06	-0.04
7_99948655_T_G	rs111963714	7	99948655	T	G	0.21	0.05	0.07	0.04	0.06	0.03
8_102483100_T_C	rs62517052	8	102483100	T	C	0.10	0.07	0.10	0.09	0.04	-0.01
8_106358620_A_T	rs12546444	8	106358620	A	T	0.10	-0.10	-0.05	-0.04	-0.01	-0.03
8_117209548_A_G	rs13267382	8	117209548	A	G	0.64	-0.04	-0.09	-0.02	-0.02	-0.04
8_120862186_A_G	rs62526620	8	120862186	A	G	0.13	0.04	0.07	0.06	0.01	0.03
8_124563705_T_C	rs35542655	8	124563705	T	C	0.15	0.05	0.04	0.03	0.11	0.03
8_124571581_G_A	rs12541094	8	124571581	G	A	0.42	0.03	0.02	0.04	0.05	0.04
8_124739913_T_G	rs7842619	8	124739913	T	G	0.40	0.04	0.04	0.04	0.06	0.07
8_128213561_C_CA	rs35961416	8	128213561	C	CA	0.41	-0.05	-0.04	-0.07	-0.04	-0.04
8_128370949_C_G	rs12550713	8	128370949	C	G	0.42	0.12	0.10	0.11	0.07	0.03
8_128372172_A_G	rs10096351	8	128372172	A	G	0.56	0.13	0.10	0.08	0.08	0.06
8_129199566_G_A	rs1016578	8	129199566	G	A	0.18	0.07	0.05	0.07	0.01	0.06
8_143669254_A_G	rs7830152	8	143669254	A	G	0.34	-0.03	-0.03	-0.02	0.04	-0.03
8_170692_T_C	rs66823261	8	170692	T	C	0.22	0.03	0.08	0.02	0.12	0.09
8_17787610_CT_C	rs3988353	8	17787610	CT	C	0.62	-0.03	-0.06	-0.06	-0.04	-0.01
8_23447496_A_G	rs1028016	8	23447496	A	G	0.64	-0.03	-0.01	-0.04	-0.04	-0.04
8_23663653_C_A	rs310295	8	23663653	C	A	0.41	0.04	0.03	0.04	0.03	-0.01
8_29509616_A_C	rs9693444	8	29509616	A	C	0.67	-0.08	-0.03	-0.04	0.01	-0.08
8_36858483_A_G	rs13365225	8	36858483	A	G	0.18	-0.08	-0.09	-0.05	-0.14	-0.05
8_76230943_A_G	rs1511243	8	76230943	A	G	0.83	0.07	0.11	0.10	0.06	0.06
8_76333056_C_T	rs72658084	8	76333056	C	T	0.09	0.12	0.12	0.21	0.14	0.06
8_76378165_G_T	rs1533366	8	76378165	G	T	0.36	-0.05	-0.04	-0.03	-0.03	-0.03
9_110303808_TAA_T	rs60037937	9	110303808	TAA	T	0.22	0.10	0.09	0.10	0.01	0.02

9_110837073_A_G	rs10816625	9	110837073	A	G	0.07	0.12	0.14	0.15	0.11	0.00
9_110837176_C_T	rs13294895	9	110837176	C	T	0.18	0.09	0.12	0.04	0.04	0.00
9_110849525_G_T	rs7848334	9	110849525	G	T	0.61	0.10	0.12	0.08	0.04	0.04
9_110885479_C_T	rs630965	9	110885479	C	T	0.64	0.13	0.11	0.13	0.05	0.01
9_119313486_A_G	rs1895062	9	119313486	A	G	0.40	-0.06	-0.05	-0.01	-0.01	-0.05
9_129424719_A_G	rs3861871	9	129424719	A	G	0.45	-0.04	-0.05	-0.03	-0.04	-0.02
9_136146597_C_T	9:136146597	9	136146597	C	T	0.27	0.05	0.05	0.01	0.00	0.06
9_21964882_CAAAA_C	rs3057314	9	21964882	CAAAA	C	0.33	0.05	0.06	0.07	0.04	0.09
9_22041998_C_G	rs17694493	9	22041998	C	G	0.14	0.03	0.01	0.05	0.10	0.10
9_36928288_T_C	rs4880038	9	36928288	T	C	0.54	0.01	0.00	0.08	0.04	0.04
9_6880263_A_G	rs10975870	9	6880263	A	G	0.29	0.04	0.03	0.02	-0.03	-0.02
9_87782211_T_C	rs665889	9	87782211	T	C	0.51	0.03	0.04	0.05	0.00	0.01
9_98362587_T_C	rs10120432	9	98362587	T	C	0.10	0.03	0.04	-0.02	0.09	0.04
10_114777670_C_T	rs10885405	10	114777670	C	T	0.47	0.05	0.02	0.03	-0.02	0.09
10_115128491_T_C	rs12250948	10	115128491	T	C	0.78	-0.08	-0.07	0.00	-0.01	-0.09
10_123095209_G_A	rs9421410	10	123095209	G	A	0.32	-0.07	-0.07	-0.01	0.00	0.02
10_123340107_A_G	rs45631580	10	123340107	A	G	0.06	-0.21	-0.11	-0.14	0.06	-0.02
10_123340431_GC_G	rs35054928	10	123340431	GC	G	0.56	-0.31	-0.28	-0.27	-0.09	-0.01
10_123349324_A_T	rs45631563	10	123349324	A	T	0.04	-0.31	-0.17	-0.24	0.01	-0.02
10_13892298_G_A	rs10796139	10	13892298	G	A	0.44	0.03	0.02	0.01	0.03	0.04
10_22032942_A_G	rs7072776	10	22032942	A	G	0.70	-0.09	-0.05	-0.07	-0.04	0.03
10_22477776_ACC_A	10:22477776	10	22477776	ACC	A	0.02	0.21	0.25	0.04	0.04	0.11
10_22861490_A_C	rs10764337	10	22861490	A	C	0.94	0.07	0.10	0.09	0.02	-0.01
10_38523626_C_A	rs2384736	10	38523626	C	A	0.37	0.04	0.02	0.03	0.03	0.05
10_5794652_A_G	10:5794652	10	5794652	A	G	0.22	0.04	0.06	0.09	0.04	0.04
10_64299890_A_G	rs10995201	10	64299890	A	G	0.15	-0.14	-0.12	-0.19	-0.16	-0.05
10_64819996_G_T	rs6479868	10	64819996	G	T	0.20	0.02	0.02	0.08	0.03	0.04
10_71335574_C_T	rs111833376	10	71335574	C	T	0.31	-0.03	-0.01	-0.02	-0.06	-0.04
10_80851257_G_T	rs719338	10	80851257	G	T	0.61	-0.10	-0.02	-0.04	-0.11	-0.02
10_80886726_A_G	rs4980029	10	80886726	A	G	0.17	0.09	0.06	0.08	0.04	0.02
10_95292187_CAA_C	rs140936696	10	95292187	CAA	C	0.82	-0.03	-0.04	-0.03	-0.10	-0.02
11_103614438_T_G	rs7125780	11	103614438	T	G	0.66	0.01	0.01	-0.01	0.10	0.05
11_108267402_C_CA	rs199504893	11	108267402	C	CA	0.42	0.01	0.00	0.03	0.02	-0.09
11_111696440_T_C	rs610437	11	111696440	T	C	0.62	-0.04	-0.03	-0.05	-0.02	0.00
11_116727936_A_T	rs625145	11	116727936	A	T	0.20	-0.03	-0.03	-0.05	-0.05	-0.04
11_122966626_A_G	rs7121616	11	122966626	A	G	0.29	-0.04	-0.03	-0.05	-0.07	-0.04
11_129243417_T_G	rs7939702	11	129243417	T	G	0.86	-0.04	-0.06	-0.05	-0.04	-0.09
11_129461016_A_G	rs11822830	11	129461016	A	G	0.61	0.05	0.03	0.05	0.06	0.07
11_18664241_T_G	rs10832963	11	18664241	T	G	0.73	0.03	0.06	0.04	0.01	0.06
11_1895708_C_A	rs4980386	11	1895708	C	A	0.38	-0.08	-0.05	-0.12	-0.11	-0.04
11_42844441_C_T	rs4472923	11	42844441	C	T	0.33	-0.02	-0.03	-0.01	-0.04	-0.05
11_433617_T_C	rs7394715	11	433617	T	C	0.80	-0.05	-0.04	-0.05	-0.09	0.00
11_44368892_G_A	rs10838267	11	44368892	G	A	0.55	0.03	0.05	0.05	0.01	0.02
11_46318032_C_G	rs77047825	11	46318032	C	G	0.06	-0.07	-0.06	-0.07	-0.17	-0.03
11_65553492_C_A	rs12287832	11	65553492	C	A	0.19	0.08	0.04	0.03	0.06	0.02
11_65572431_G_A	rs10896047	11	65572431	G	A	0.48	-0.06	-0.04	-0.04	-0.06	0.01
11_69328130_A_T	rs35039974	11	69328130	A	T	0.21	-0.12	-0.07	-0.05	0.03	0.01
11_69330983_G_A	rs661204	11	69330983	G	A	0.14	0.32	0.16	0.17	-0.01	0.01
11_69331418_C_T	rs78540526	11	69331418	C	T	0.09	0.41	0.21	0.21	0.01	-0.03
11_803017_A_G	rs6597981	11	803017	A	G	0.52	0.04	0.02	0.07	0.09	0.06
12_103097887_C_T	12:103097887	12	103097887	C	T	0.12	0.05	0.03	0.04	-0.08	0.05
12_111600134_G_T	12:111600134	12	111600134	G	T	0.37	-0.04	-0.06	-0.03	-0.06	-0.03
12_115108136_T_C	12:115108136	12	115108136	T	C	0.27	0.05	0.07	0.07	0.02	0.02
12_115796577_A_G	12:115796577	12	115796577	A	G	0.19	-0.07	0.01	-0.04	-0.06	0.01
12_115835836_T_C	rs2454399	12	115835836	T	C	0.41	-0.10	-0.06	-0.09	-0.08	-0.02
12_120832146_C_T	12:120832146	12	120832146	C	T	0.16	0.05	0.06	0.02	0.06	0.04
12_14413931_G_C	rs12422552	12	14413931	G	C	0.27	0.05	0.03	0.07	0.06	0.06

12_28149568_C_T	rs788458	12	28149568	C	T	0.11	-0.15	-0.13	-0.14	-0.14	-0.18
12_28174817_C_T	rs7297051	12	28174817	C	T	0.23	-0.13	-0.11	-0.11	-0.13	-0.18
12_28347382_C_T	12:28347382	12	28347382	C	T	0.21	-0.07	-0.08	-0.06	-0.07	-0.11
12_29140260_G_A	12:29140260	12	29140260	G	A	0.92	0.08	0.03	0.04	0.10	0.07
12_293626_A_G	12:293626	12	293626	A	G	0.37	0.03	0.05	0.05	0.05	0.02
12_57146069_T_G	rs2277339	12	57146069	T	G	0.10	-0.05	-0.05	-0.03	-0.03	-0.05
12_70798355_A_T	12:70798355	12	70798355	A	T	0.18	0.04	0.04	0.07	0.00	0.01
12_83064195_G_GA	12:83064195	12	83064195	G	GA	0.10	0.06	0.07	0.07	0.10	0.05
12_85004551_C_T	12:85004551	12	85004551	C	T	0.50	0.02	0.03	0.05	0.07	0.05
12_96027759_A_G	rs17356907	12	96027759	A	G	0.29	-0.10	-0.07	-0.09	-0.02	-0.09
13_32839990_G_A	rs56404467	13	32839990	G	A	0.02	0.10	0.24	0.15	0.20	0.30
13_32972626_A_T	rs11571833	13	32972626	A	T	0.01	0.16	0.40	0.39	0.46	0.48
13_43501356_A_G	rs9315973	13	43501356	A	G	0.83	0.03	0.02	0.02	-0.02	0.09
13_73806982_T_C	rs12870942	13	73806982	T	C	0.32	0.03	0.04	0.08	0.07	0.07
13_73960952_A_G	rs2181965	13	73960952	A	G	0.77	0.04	0.03	0.04	0.11	0.08
14_105213978_T_G	rs4983544	14	105213978	T	G	0.47	0.03	0.02	0.06	0.01	0.05
14_37128564_C_A	rs34914085	14	37128564	C	A	0.20	-0.10	-0.07	-0.01	-0.06	-0.03
14_37228504_C_T	rs2253012	14	37228504	C	T	0.45	0.06	0.03	0.03	0.01	0.04
14_68660428_T_C	rs2588809	14	68660428	T	C	0.83	-0.09	-0.09	-0.08	0.02	0.00
14_68979835_T_C	rs11624333	14	68979835	T	C	0.25	-0.12	-0.06	-0.12	-0.04	-0.09
14_91751788_TC_T	rs11341843	14	91751788	TC	T	0.70	0.05	0.05	0.09	0.08	0.00
14_91841069_A_G	rs941764	14	91841069	A	G	0.35	0.06	0.06	0.10	0.07	0.02
14_93070286_C_T	rs78440108	14	93070286	C	T	0.17	-0.06	-0.06	-0.05	-0.09	-0.06
15_100905819_A_C	rs144767203	15	100905819	A	C	0.11	-0.05	-0.07	-0.09	-0.03	-0.06
15_46680811_C_A	rs187010898	15	46680811	C	A	0.01	-0.15	-0.17	-0.37	-0.26	-0.10
15_50694306_A_G	rs4774565	15	50694306	A	G	0.34	-0.04	-0.04	-0.01	0.03	-0.05
15_66630569_G_A	rs8042593	15	66630569	G	A	0.64	-0.03	-0.02	-0.02	0.01	-0.03
15_67457698_A_G	rs35874463	15	67457698	A	G	0.05	0.09	0.08	0.00	-0.05	0.06
15_75750383_T_C	rs8035987	15	75750383	T	C	0.26	-0.05	-0.03	0.03	-0.02	-0.04
15_91512267_G_T	rs2290202	15	91512267	G	T	0.13	-0.05	-0.15	-0.14	-0.11	-0.06
16_10706580_G_A	rs34872983	16	10706580	G	A	0.07	-0.08	-0.02	-0.09	-0.14	-0.01
16_23007047_G_T	rs75753503	16	23007047	G	T	0.02	0.14	0.05	0.09	-0.02	0.07
16_4008542_CAAAAA_C	rs57920543	16	4008542	CAAAAA	C	0.82	-0.04	-0.03	0.01	-0.10	-0.06
16_4106788_C_A	rs11076805	16	4106788	C	A	0.26	-0.02	-0.02	-0.02	-0.04	-0.06
16_52538825_C_A	rs35668161	16	52538825	C	A	0.28	0.24	0.21	0.22	0.21	0.12
16_52599188_C_T	rs4784227	16	52599188	C	T	0.27	0.25	0.20	0.22	0.21	0.11
16_53809123_C_T	rs55872725	16	53809123	C	T	0.41	-0.06	-0.06	-0.08	-0.09	-0.07
16_53861139_C_T	rs6499648	16	53861139	C	T	0.76	-0.03	-0.03	-0.03	-0.10	-0.07
16_53861592_G_A	rs7184573	16	53861592	G	A	0.36	-0.05	-0.04	-0.01	-0.10	-0.04
16_54682064_G_A	rs28539243	16	54682064	G	A	0.49	0.05	0.04	0.04	0.05	0.02
16_6963972_C_G	rs12709163	16	6963972	C	G	0.79	0.00	-0.02	0.05	0.07	0.03
16_80648296_A_G	rs7500067	16	80648296	A	G	0.24	0.09	0.09	0.10	0.03	0.04
16_85145977_T_C	rs9931038	16	85145977	T	C	0.49	-0.02	0.00	0.03	-0.05	-0.07
16_87086492_T_C	rs12449271	16	87086492	T	C	0.25	-0.05	-0.04	-0.05	-0.06	-0.03
17_29168077_G_T	rs79461387	17	29168077	G	T	0.26	-0.04	-0.04	-0.06	-0.06	-0.04
17_39251123_T_C	rs150537328	17	39251123	T	C	0.07	0.07	0.05	0.02	0.18	0.14
17_40127060_T_C	rs11296	17	40127060	T	C	0.06	-0.02	-0.10	-0.06	0.06	0.13
17_40485239_G_T	rs17881320	17	40485239	G	T	0.08	-0.05	0.01	-0.02	-0.16	-0.10
17_40744470_G_A	rs149370081	17	40744470	G	A	0.01	0.24	0.14	0.07	0.15	0.17
17_43212339_C_CT	rs71363517	17	43212339	C	CT	0.23	0.03	0.02	0.01	0.03	0.06
17_44283858_G_A	17:44283858	17	44283858	G	A	0.19	-0.05	-0.03	-0.09	-0.10	-0.02
17_53209774_A_C	rs2787486	17	53209774	A	C	0.29	-0.11	-0.04	-0.08	-0.04	-0.02
17_77781725_A_G	rs745570	17	77781725	A	G	0.50	-0.04	-0.03	-0.06	-0.05	-0.05
18_11696613_C_T	rs16976596	18	11696613	C	T	0.14	-0.02	0.00	-0.01	-0.10	-0.06
18_20634253_C_T	rs11665269	18	20634253	C	T	0.64	-0.04	-0.06	-0.02	-0.05	-0.01
18_24125857_T_C	rs1111207	18	24125857	T	C	0.43	0.04	0.05	0.06	-0.02	0.04
18_24337424_C_G	rs527616	18	24337424	C	G	0.63	0.05	0.09	0.04	0.06	0.03

18_24518050_AT_A	rs35369219	18	24518050	AT	A	0.27	-0.08	-0.05	-0.06	0.02	0.03
18_25407513_C_G	rs8092192	18	25407513	C	G	0.71	0.02	0.02	0.07	0.08	0.07
18_29981526_G_A	rs72931898	18	29981526	G	A	0.04	-0.08	-0.14	-0.11	-0.07	-0.14
18_42411803_G_C	rs9954058	18	42411803	G	C	0.07	-0.13	-0.07	-0.08	-0.10	-0.01
18_42888797_T_C	rs9952980	18	42888797	T	C	0.34	-0.05	-0.02	-0.08	0.01	-0.05
19_13249921_G_T	rs117922601	19	13249921	G	T	0.05	0.13	0.10	0.00	0.03	0.13
19_17393925_C_A	rs56069439	19	17393925	C	A	0.30	-0.01	0.05	0.04	-0.01	0.23
19_18569492_C_T	rs10164323	19	18569492	C	T	0.34	-0.09	-0.02	-0.06	-0.06	-0.06
19_19517054_C_CGGGCG	rs140702307	19	19517054	C	CGGGCG	0.36	0.03	0.05	0.02	0.04	0.03
19_44283031_T_C	rs56681946	19	44283031	T	C	0.36	0.07	0.06	0.06	0.10	0.07
19_46166073_T_C	rs4399645	19	46166073	T	C	0.60	-0.03	-0.05	-0.03	-0.02	-0.01
19_55816678_C_T	rs1172821	19	55816678	C	T	0.36	-0.03	-0.04	0.00	-0.07	-0.03
20_11379842_T_C	rs1154723	20	11379842	T	C	0.95	0.07	0.02	0.08	0.26	-0.01
20_41613706_C_G	rs6030585	20	41613706	C	G	0.79	0.03	0.01	-0.01	0.04	0.06
20_52296849_G_A	rs13039563	20	52296849	G	A	0.24	0.06	0.04	0.05	0.01	0.00
20_5948227_G_A	rs16991615	20	5948227	G	A	0.07	0.07	0.09	0.15	0.06	0.08
21_16364756_T_G	rs2822999	21	16364756	T	G	0.18	0.07	0.09	0.06	0.04	0.05
21_16566350_A_G	rs2823130	21	16566350	A	G	0.09	0.09	0.05	0.09	0.06	0.01
21_16574455_C_A	rs2403907	21	16574455	C	A	0.31	-0.11	-0.06	-0.08	-0.06	-0.01
21_47762932_G_A	rs4818836	21	47762932	G	A	0.04	0.09	0.11	0.12	0.11	0.07
22_19766137_C_T	rs9798754	22	19766137	C	T	0.38	-0.05	-0.03	0.00	-0.07	-0.02
22_29121087_A_G	rs17879961	22	29121087	A	G	0.01	0.42	0.07	0.34	0.35	-0.66
22_29135543_G_A	rs5997390	22	29135543	G	A	0.09	0.10	0.05	0.08	0.08	0.01
22_29203724_C_T	rs34134147	22	29203724	C	T	0.02	0.17	0.34	0.34	-0.06	0.02
22_29551872_A_G	rs132289	22	29551872	A	G	0.98	-0.19	-0.35	-0.37	-0.09	-0.09
22_38583315_AAAAG_AAAAGAAAG	rs373038216	22	38583315	AAAAG	AAAAGAAAG	0.28	-0.07	-0.05	-0.02	-0.02	0.00
22_39343916_T_A	rs5750715	22	39343916	T	A	0.26	0.06	0.07	0.03	0.04	0.03
22_40904707_CT_C	rs66987842	22	40904707	CT	C	0.12	0.13	0.04	0.11	0.14	0.12
22_43433100_C_T	rs9611990	22	43433100	C	T	0.11	-0.05	-0.04	-0.06	-0.14	-0.02
22_45319953_G_A	rs112855987	22	45319953	G	A	0.41	-0.01	-0.01	-0.04	-0.01	-0.05
22_46283297_G_A	rs28512361	22	46283297	G	A	0.11	0.06	0.11	0.07	0.13	0.09
2_67881757_G_A ³	rs9712235	2	67881757	G	A	0.74	-0.04	-0.02	0.00	-0.01	-0.08
2_69392128_G_A ³	rs4602255	2	69392128	G	A	0.45	0.03	0.04	0.01	0.06	0.04
3_16778867_A_G ³	rs1375631	3	16778867	A	G	0.50	0.03	0.01	0.02	0.00	0.06
3_156535958_AT_A ³	rs34052812	3	156535958	AT	A	0.67	0.04	0.05	0.05	0.02	0.04
7_74341926_G_C ³	rs188092014	7	74341926	G	C	0.19	0.04	0.04	0.03	0.08	0.04
8_25831778_C_T ³	rs13256025	8	25831778	C	T	0.21	0.04	0.06	0.04	0.08	0.02
8_116679547_A_G ³	rs13277568	8	116679547	A	G	0.37	-0.05	-0.06	-0.03	0.01	-0.01
9_106856793_G_C ³	rs4742903	9	106856793	G	C	0.56	0.01	0.04	0.07	0.00	0.05
17_70405095_C_G ³	rs11652463	17	70405095	C	G	0.30	-0.03	-0.05	-0.04	-0.06	-0.06
4_1986972_A_G ³	rs495367	4	1986972	A	G	0.35	0.05	0.05	0.04	0.06	0.01
5_67424121_C_CTG ³	rs138044103	5	67424121	C	CTG	0.48	0.05	-0.01	0.02	0.02	-0.03
11_120233626_A_G ³	rs7924772	11	120233626	A	G	0.39	0.05	0.01	-0.03	-0.05	0.04
17_7571752_T_G ³	rs78378222	17	7571752	T	G	0.01	0.12	0.03	0.26	0.18	-0.44
18_10354649_A_C ³	rs206435	18	10354649	A	C	0.51	-0.03	0.02	0.02	0.05	0.05
20_39248265_G_A ³	rs6065254	20	39248265	G	A	0.41	-0.04	-0.02	-0.04	0.00	0.03
6_33239869_C_T ³	rs17215231	6	33239869	C	T	0.08	-0.01	-0.05	0.04	0.05	-0.22
12_121435475_G_A ³	rs121435475	12	121435475	G	A	0.36	-0.02	0.00	-0.06	-0.05	-0.03

¹ The variant name coded as chromosome_position_reference allele_effect allele

² Effect allele frequency estimated on OncoArray data

³ Seventeen out of the 32 new variants that are independent with previous reported 313 SNPs for overall and ER-specific breast cancer PRS (Mavaddat, Nasim, et al. The American Journal of Human Genetics 104.1 (2019): 21-34)