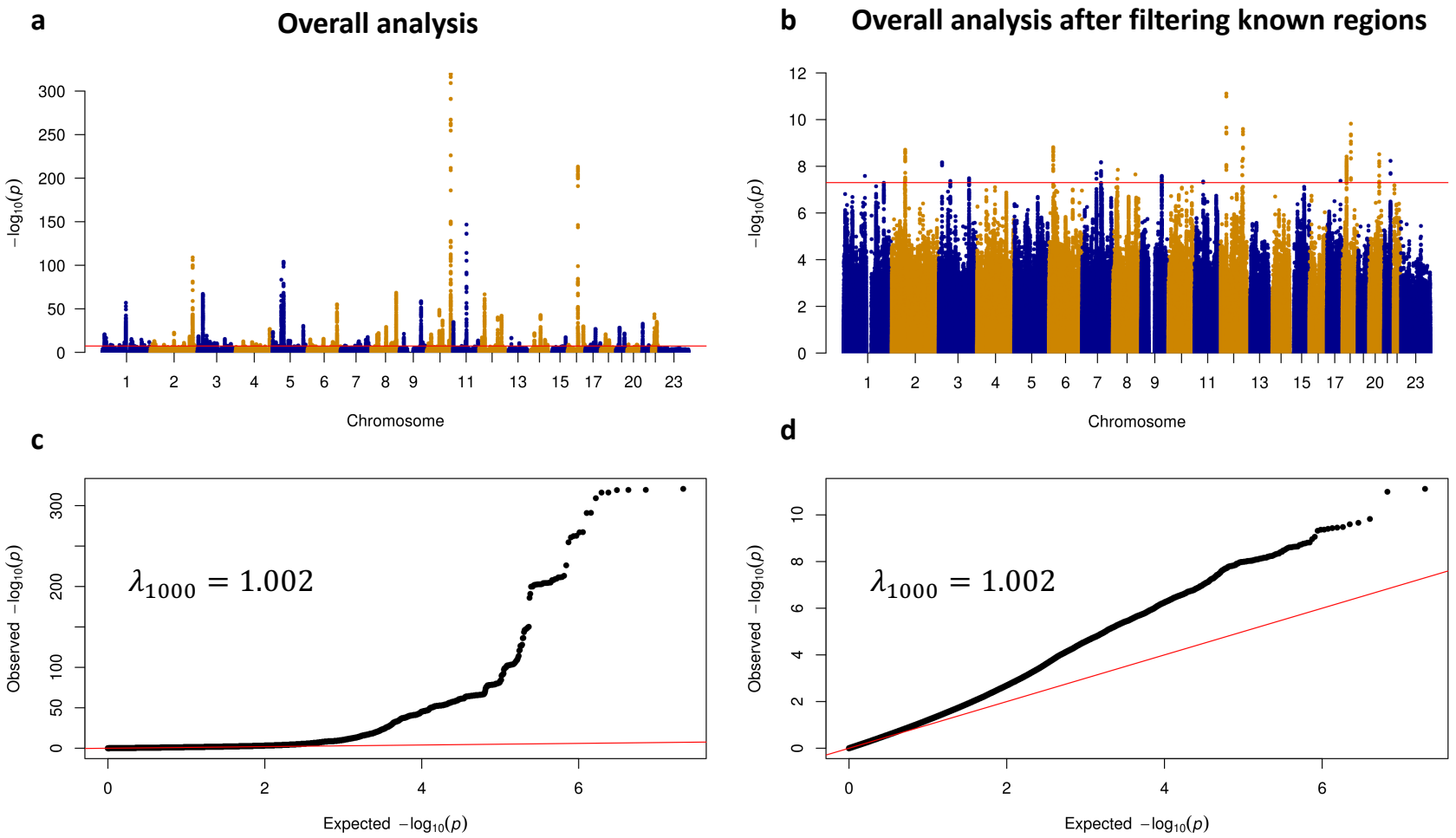
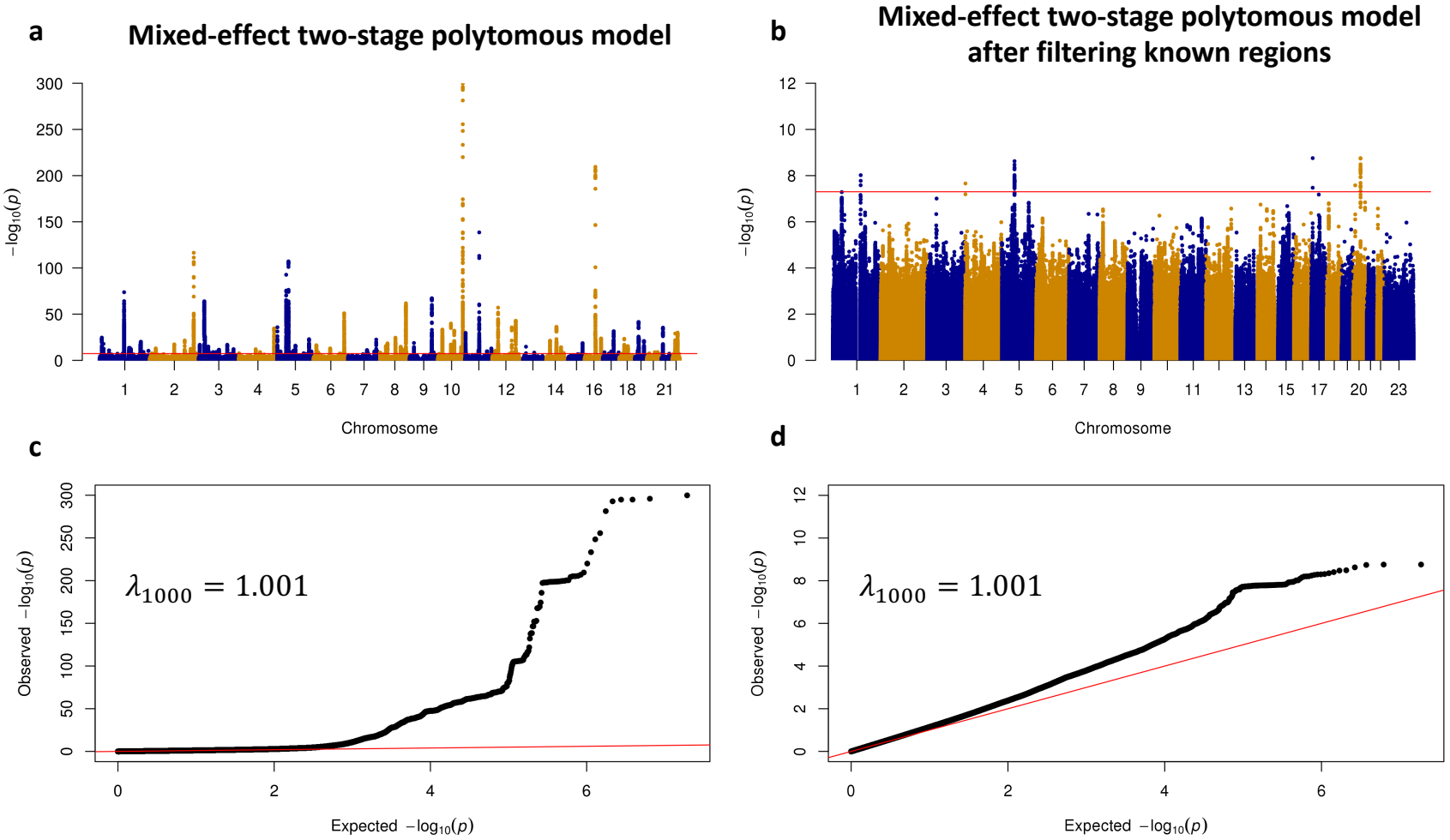
Supplementary figure 1. Variants associations with overall breast cancer risk identified using standard logistic regression (n = 133,384 cases, n = 113,789 controls). **a)** Manhattan plot showing -$\log_{10}P$ values for variant associations with breast cancer risk. **b)** Manhattan plot after excluding previous known regions (Online Methods) **c)** Quantile-Quantile (Q-Q) plot of observed P-values versus expected P-values for all variants. **d)** QQ plot[1] 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 = 5x 10^{-8}).



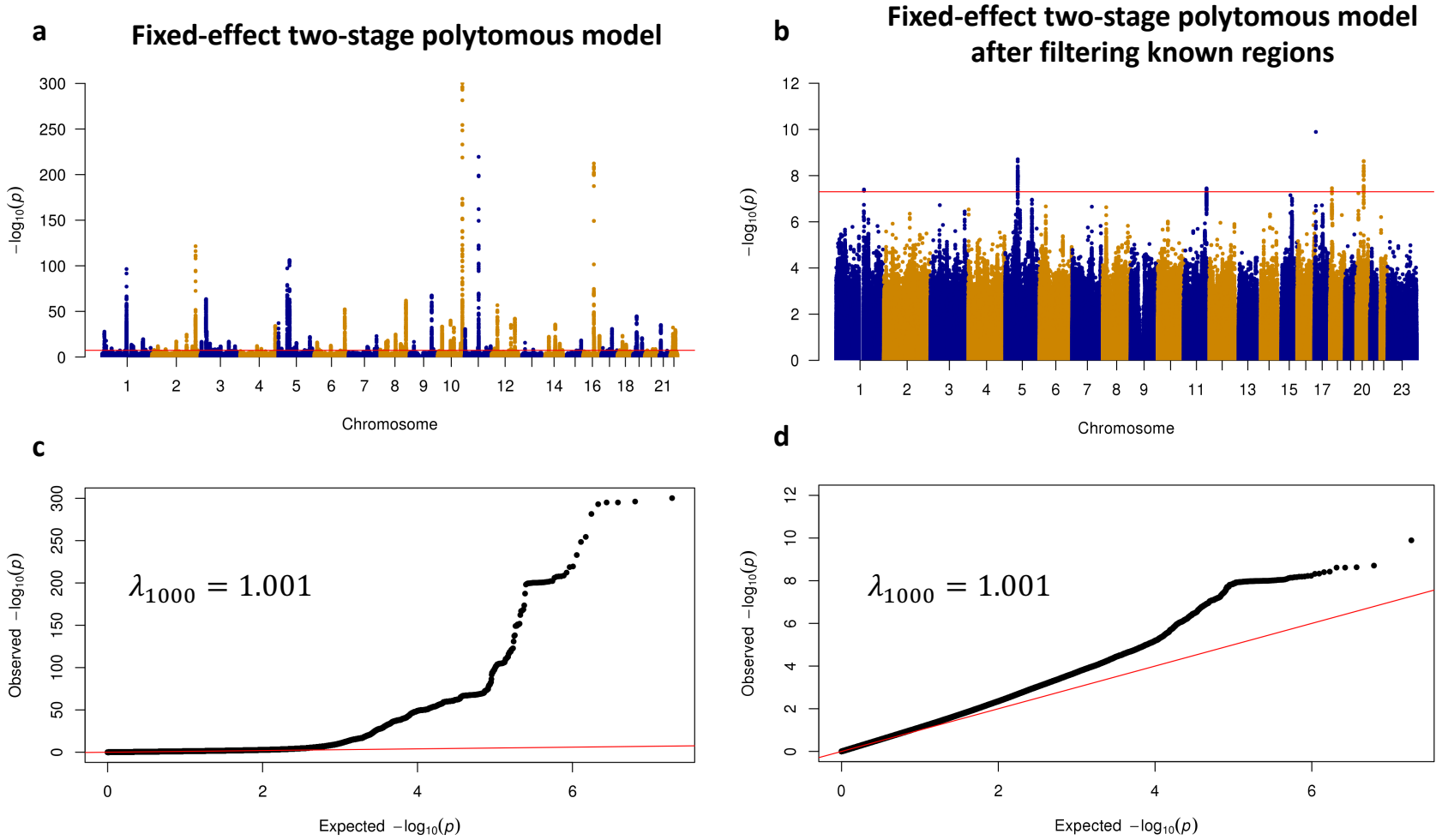
1) λ_{1000} scale the genomic inflation factor λ to a study with sample size of 1000 cases and 1000 controls using the formula $\lambda_{1000} = 1 + 500 * (\lambda - 1)/(\frac{1}{n_{cases}} + \frac{1}{n_{control}})$

Supplementary figure 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 plot[1] 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 x 10^{-8}).



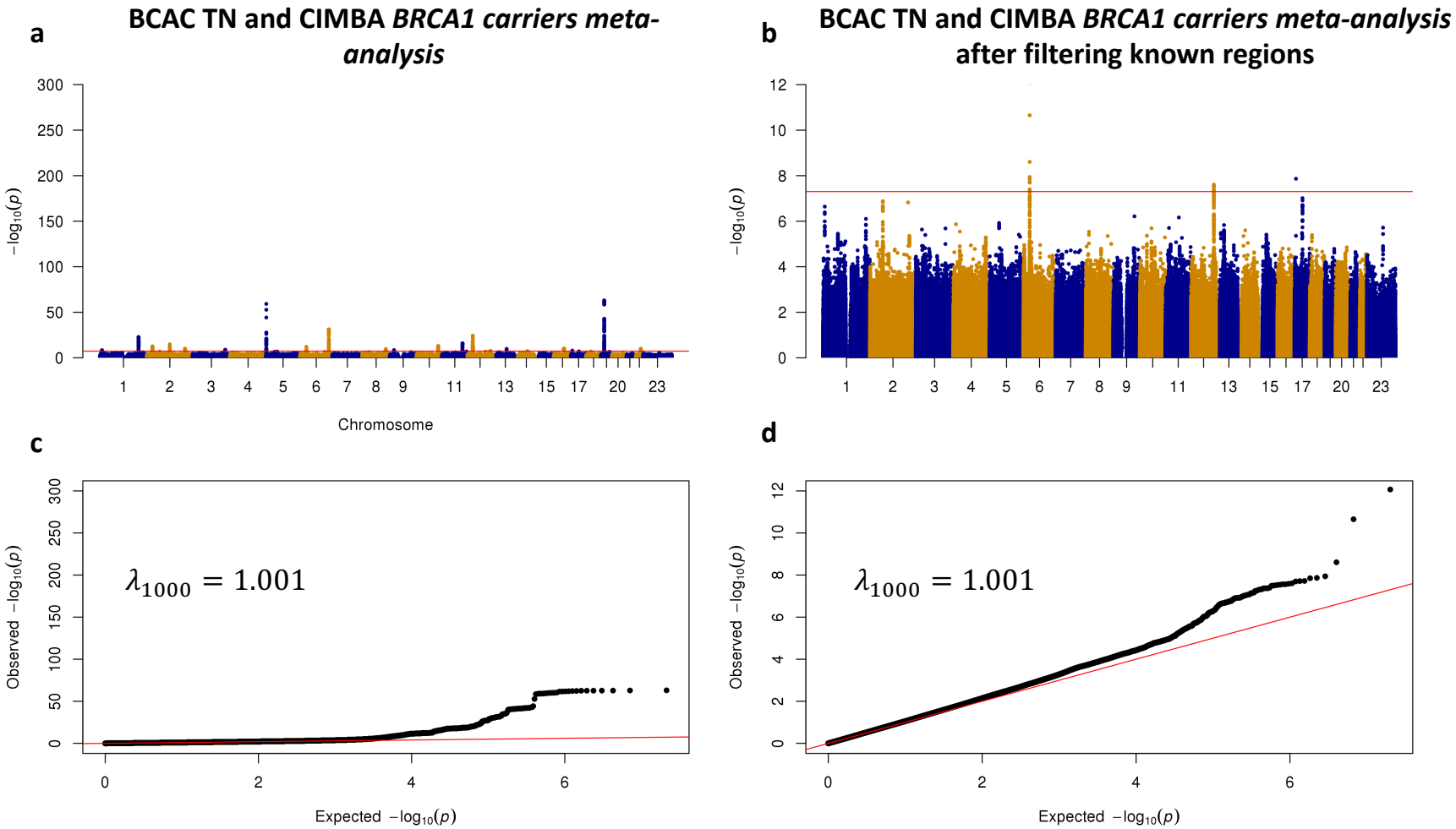
1) λ_{1000} scale the genomic inflation factor λ to a study with sample size of 1000 cases and 1000 controls using the formula $\lambda_{1000} = 1 + 500 * (\lambda - 1)/(\frac{1}{n_{cases}} + \frac{1}{n_{control}})$

Supplementary figure 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 plot[1] 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 = 5x 10^{-8}).



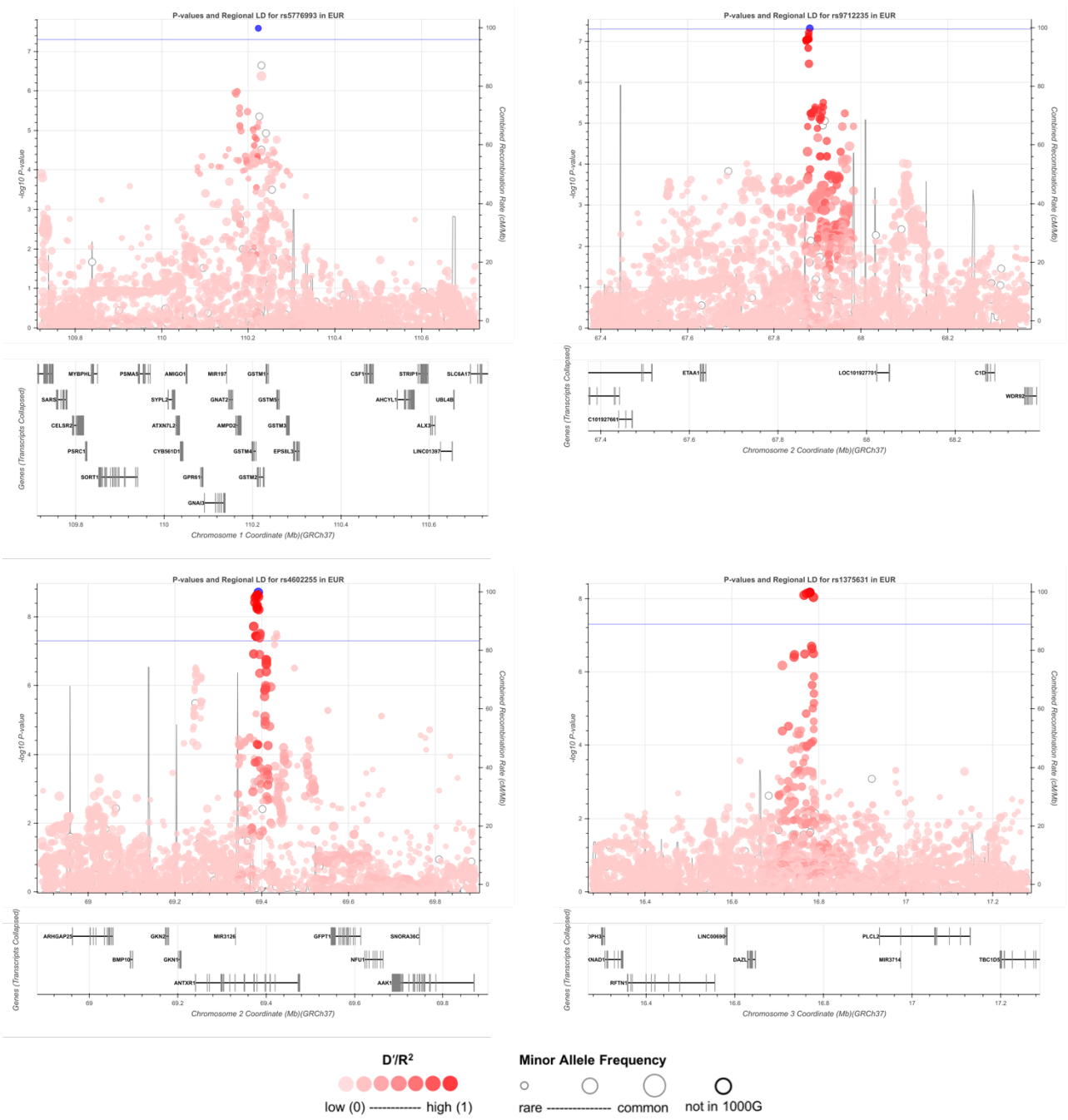
1) λ_{1000} scale the genomic inflation factor λ to a study with sample size of 1000 cases and 1000 controls using the formula $\lambda_{1000} = 1 + 500 * (\lambda - 1)/(\frac{1}{n_{cases}} + \frac{1}{n_{control}})$

Supplementary figure 4. Variant association with triple-negative 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 breast cancer risk. **b)** Manhattan plot showing -$\log_{10}$P values for variant associations with triple-negative breast cancer risk after excluding previously known regions (Online Methods). **c)** QQ plot[1] 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 = 5x 10^{-8}).

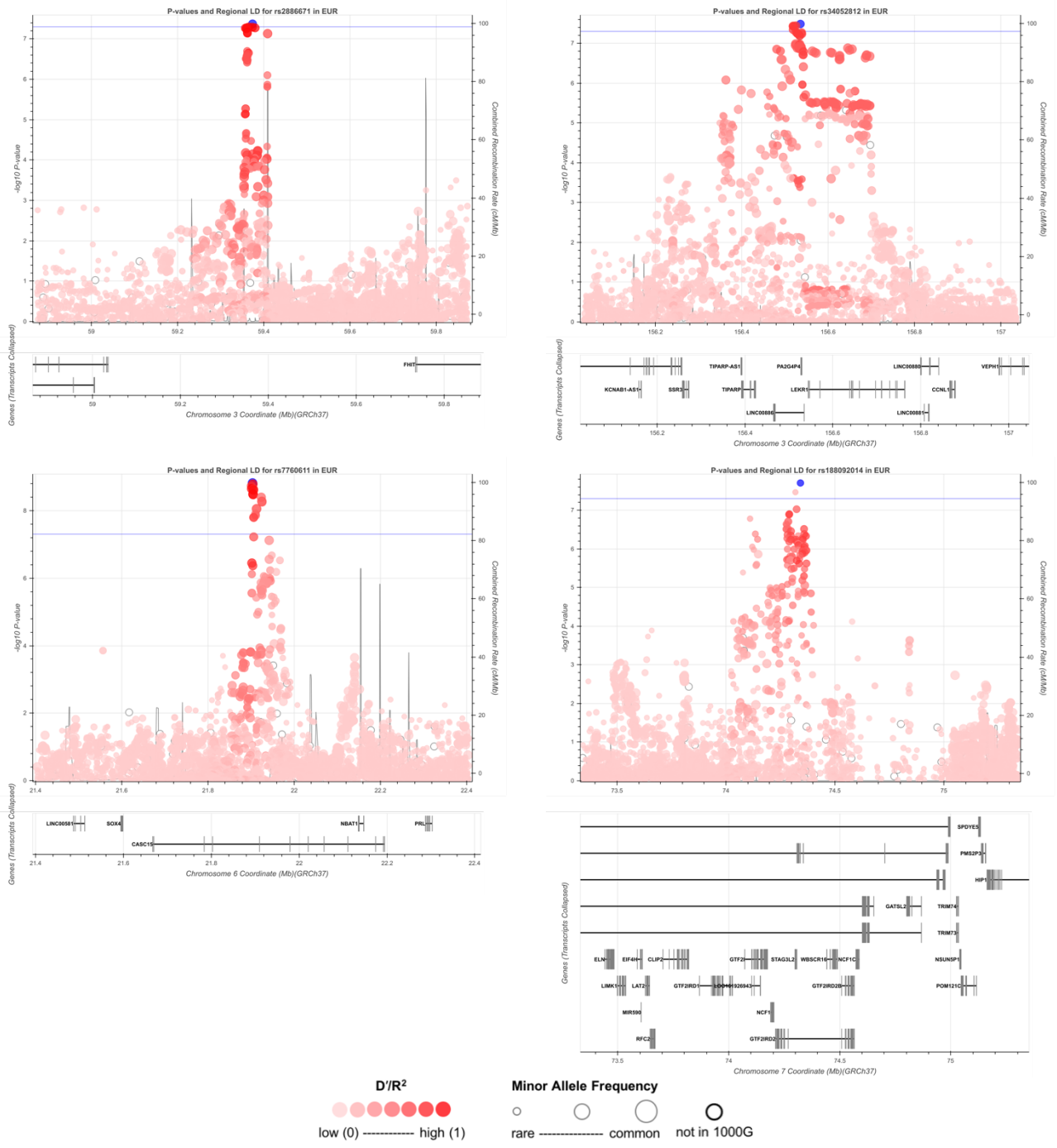


1) λ_{1000} scale the genomic inflation factor λ to a study with sample size of 1000 cases and 1000 controls using the formula $\lambda_{1000} = 1 + 500 * (\lambda - 1)/(\frac{1}{n_{cases}} + \frac{1}{n_{control}})$

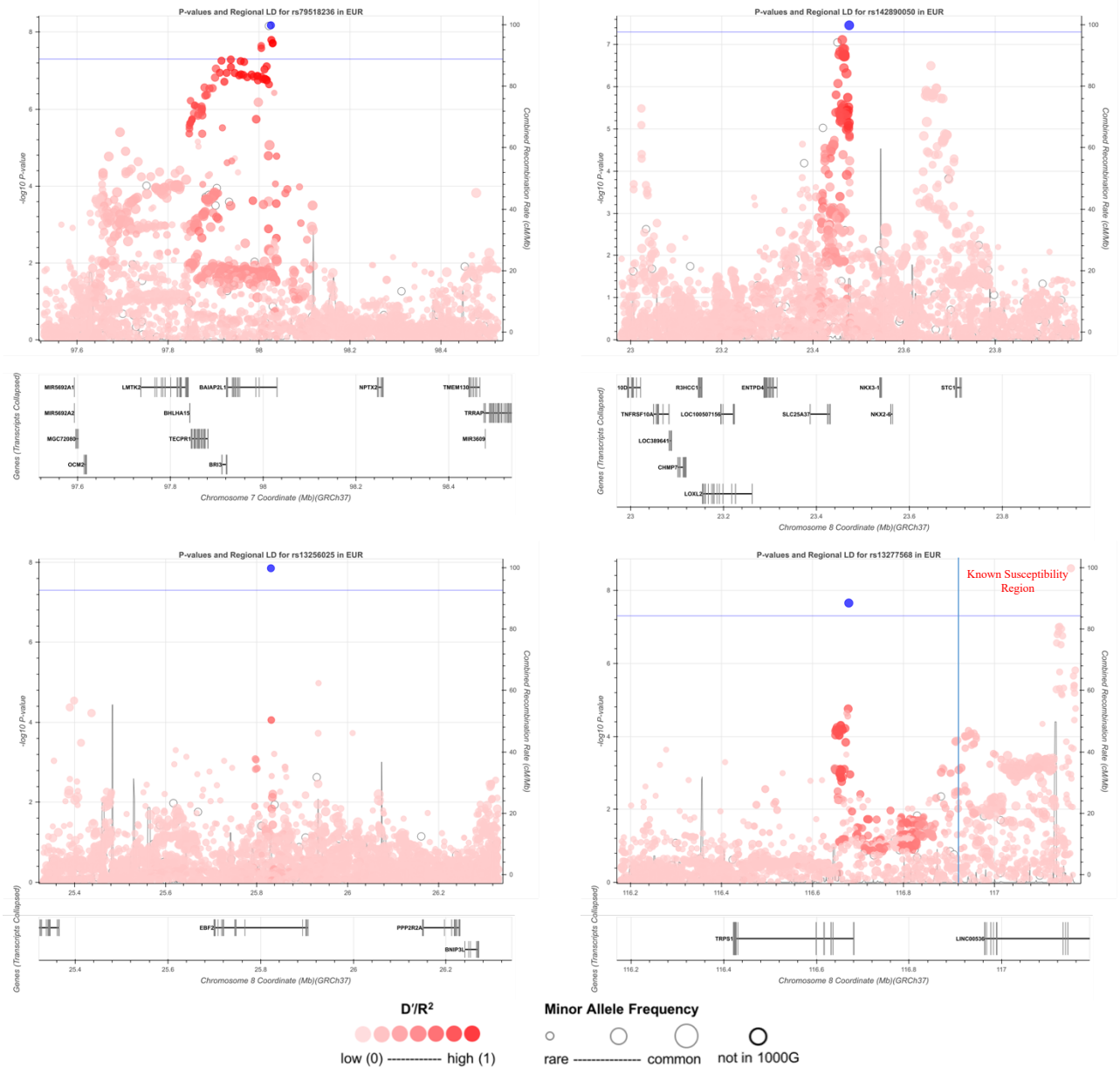
Supplementary figure 5. Regional plots of the 32 identified breast cancer variants. The first 22 variants were identified through standard logistic regression (n = 133,384 cases, n = 113,789 controls), the following eight variants were identified through two-stage polytomous regression (n = 106,278 invasive cases, n = 91,477 controls), the last two variants were identified through meta-analysis of BCAC triple-negative 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}).



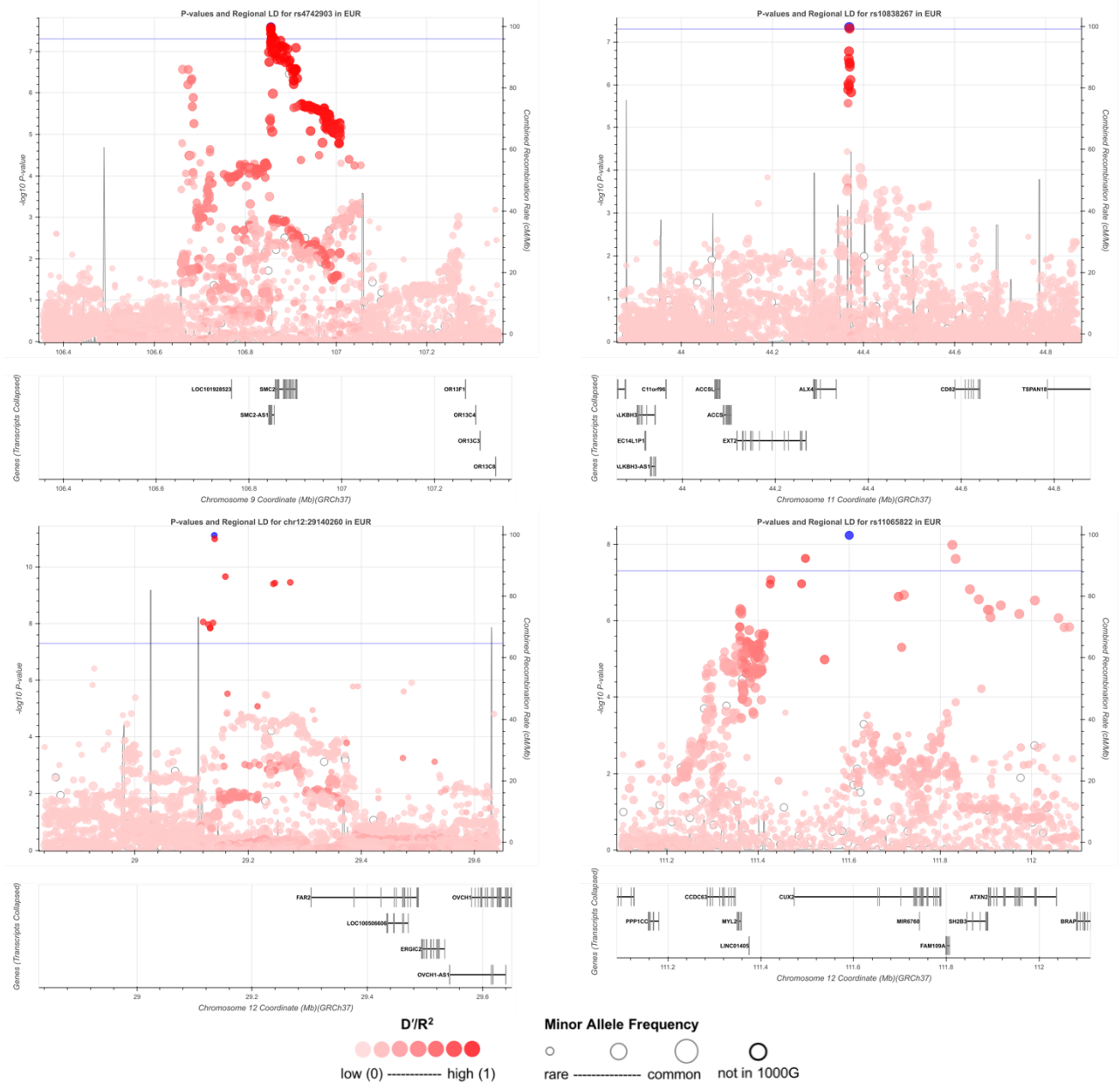
Supplementary figure 5 continued. Regional plots of the 32 identified breast cancer variants. The first 22 variants were identified through standard logistic regression (n = 133,384 cases, n = 113,789 controls), the following eight variants were identified through two-stage polytomous regression (n = 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}).



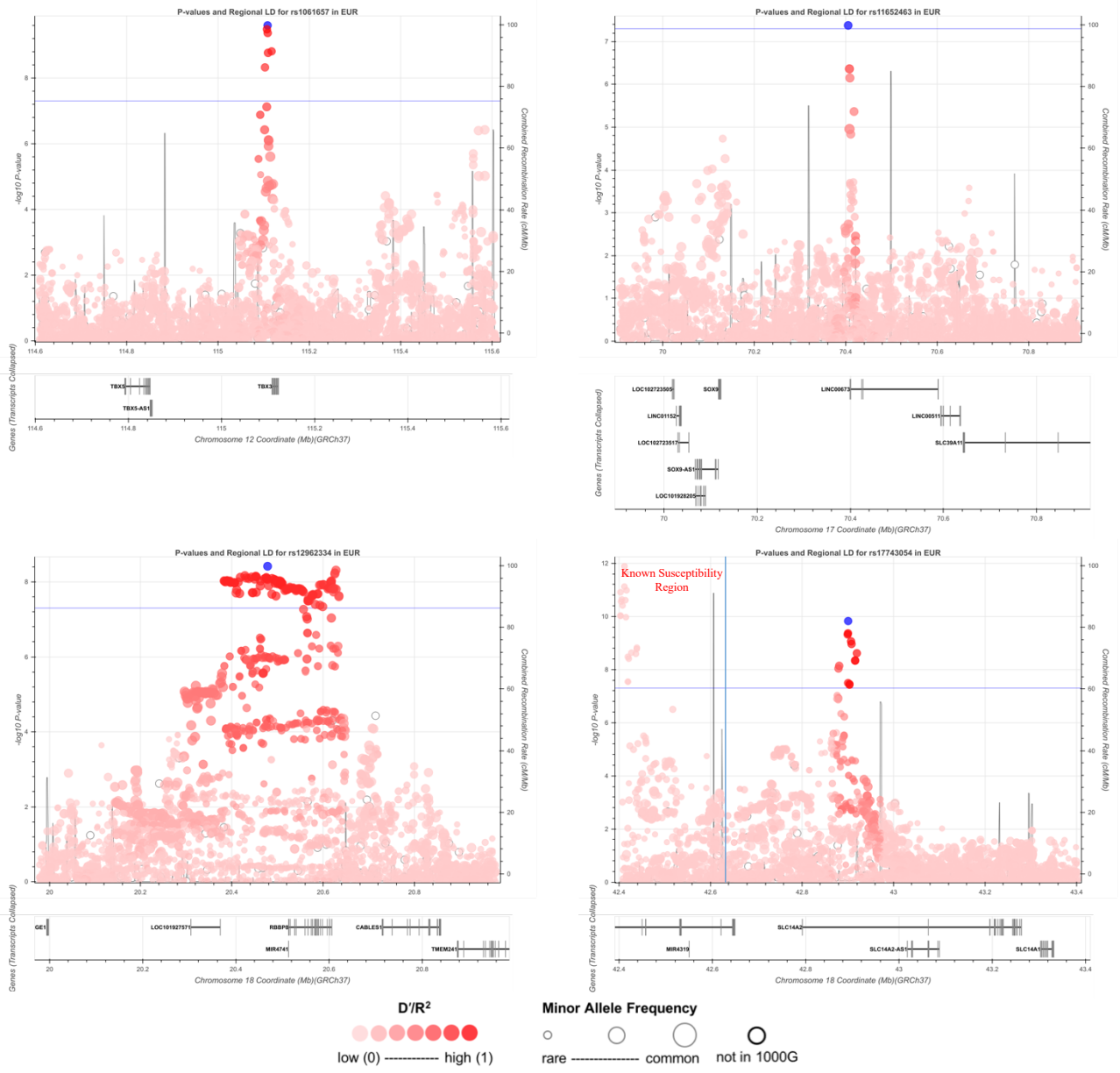
Supplementary figure 5 continued. Regional plots of the 32 identified breast cancer variants. The first 22 variants were identified through standard logistic regression (n = 133,384 cases, n = 113,789 controls), the following eight variants were identified through two-stage polytomous regression (n = 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}).



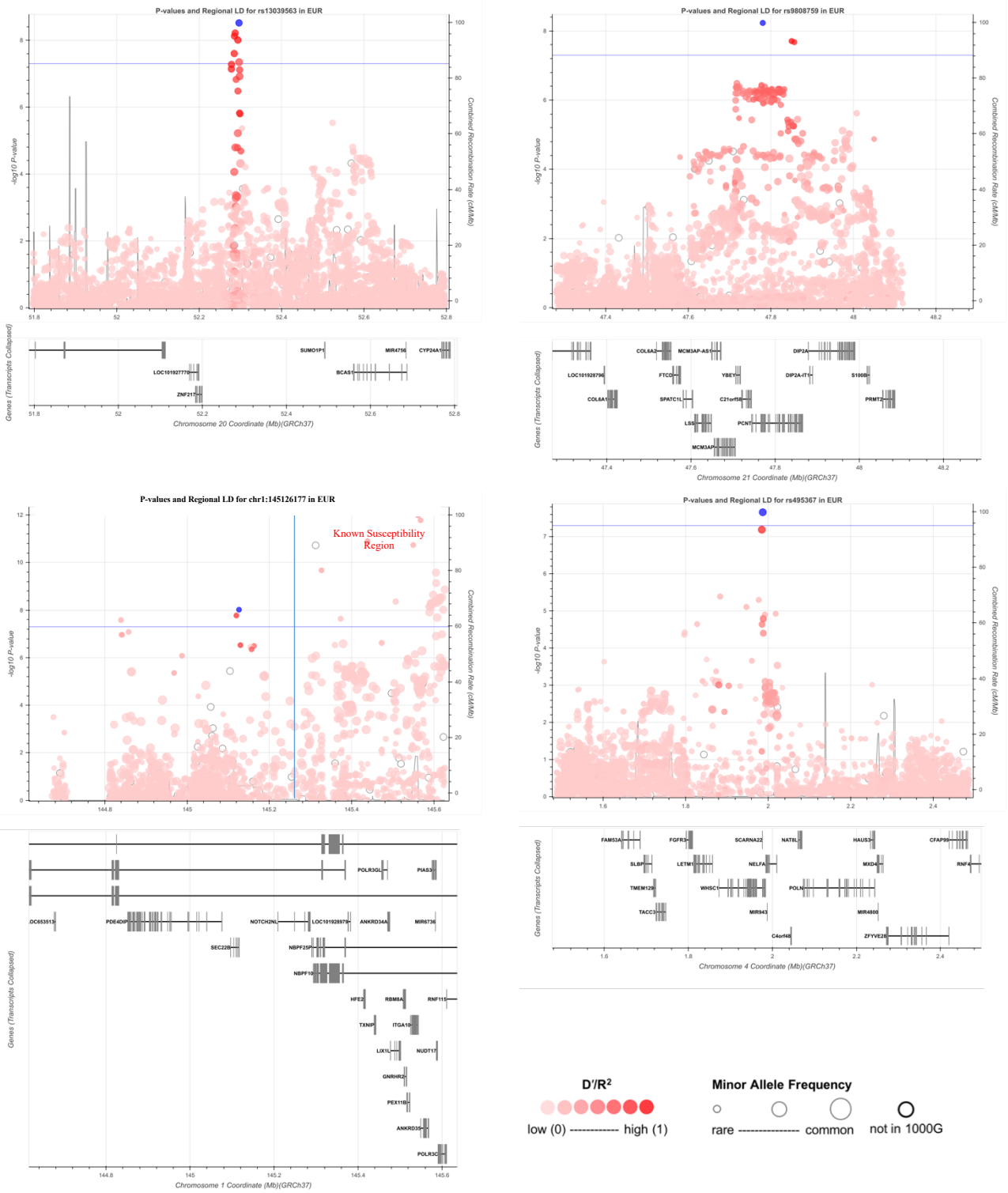
Supplementary figure 5 continued. Regional plots of the 32 identified breast cancer variants. The first 22 variants were identified through standard logistic regression (n = 133,384 cases, n = 113,789 controls), the following eight variants were identified through two-stage polytomous regression (n = 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}).



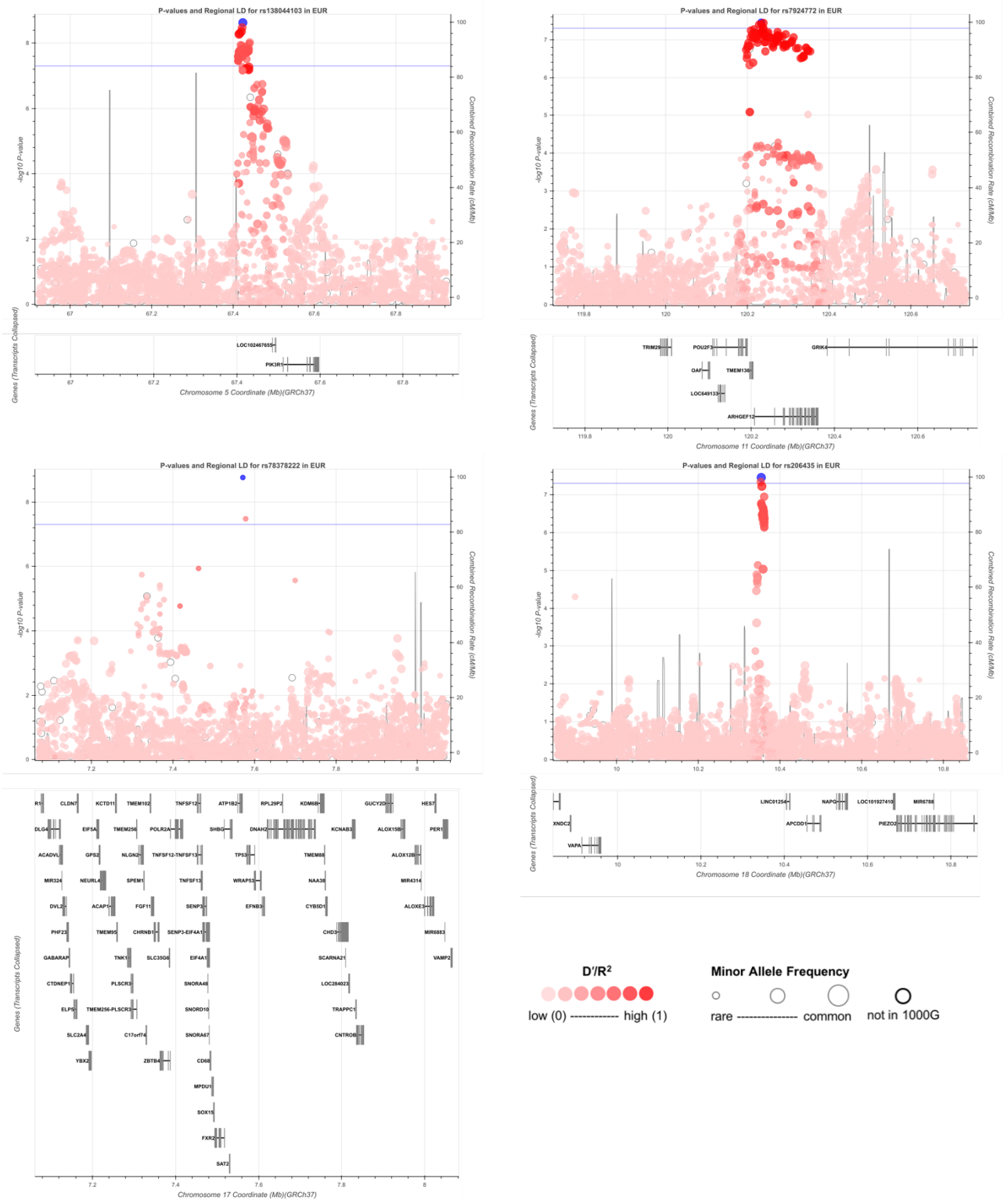
Supplementary figure 5 continued. Regional plots of the 32 identified breast cancer variants. The first 22 variants were identified through standard logistic regression (n = 133,384 cases, n = 113,789 controls), the following eight variants were identified through two-stage polytomous regression (n = 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}).



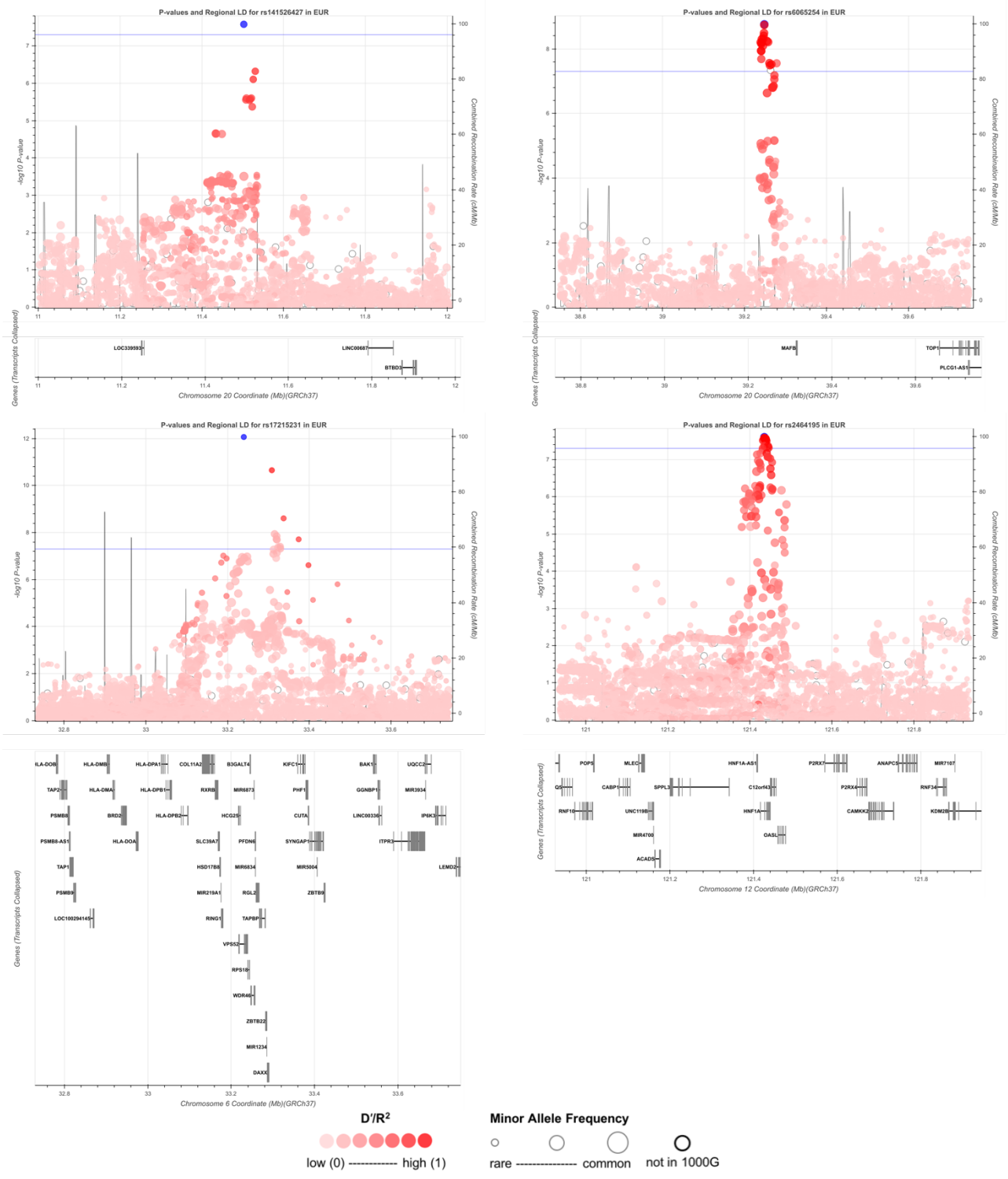
Supplementary figure 5 continued. Regional plots of the 32 identified breast cancer variants. The first 22 variants were identified through standard logistic regression (n = 133,384 cases, n = 113,789 controls), the following eight variants were identified through two-stage polytomous regression (n = 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}).



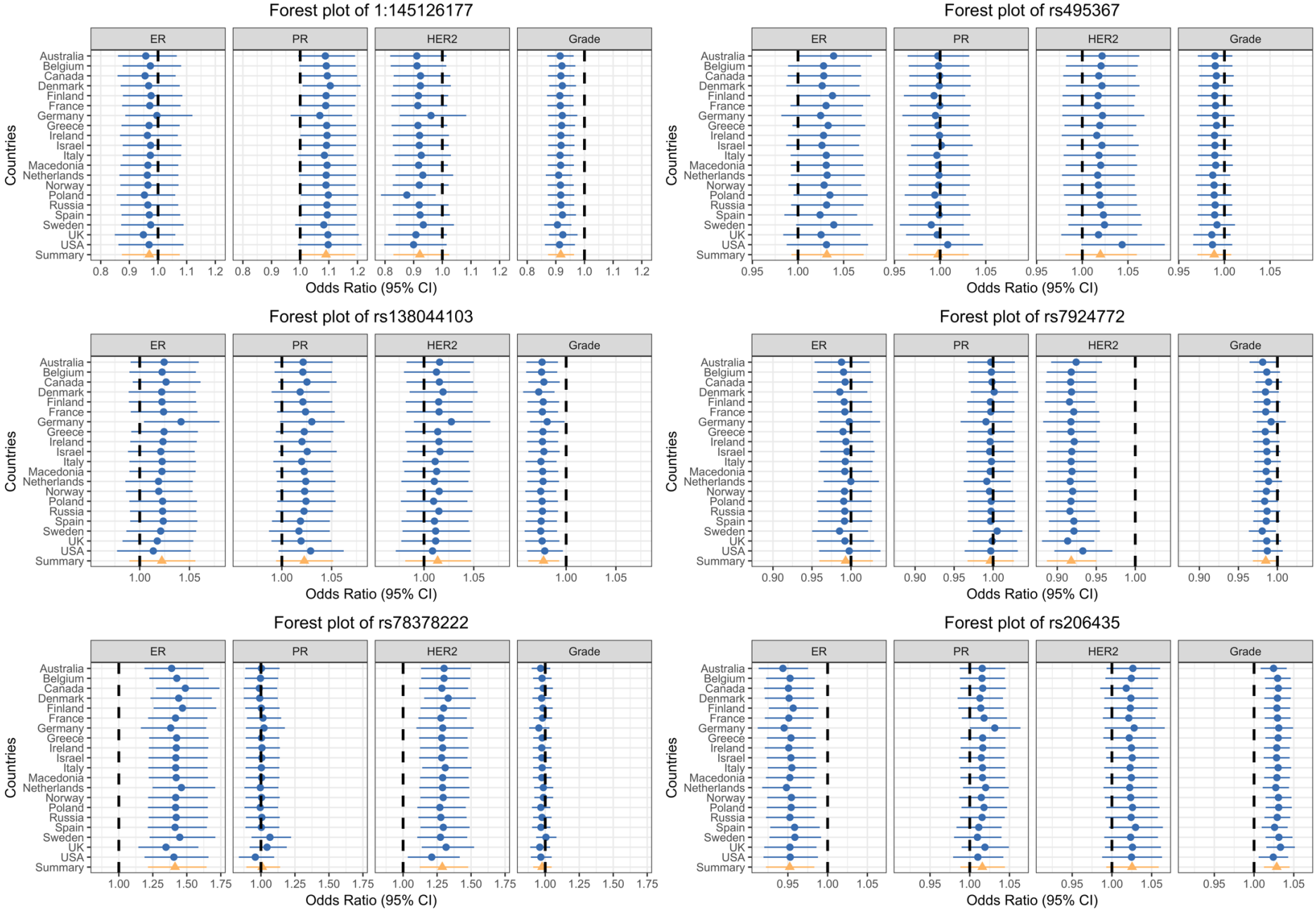
Supplementary figure 5 continued. Regional plots of the 32 identified breast cancer variants. The first 22 variants were identified through standard logistic regression (n = 133,384 cases, n = 113,789 controls), the following eight variants were identified through two-stage polytomous regression (n = 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}).

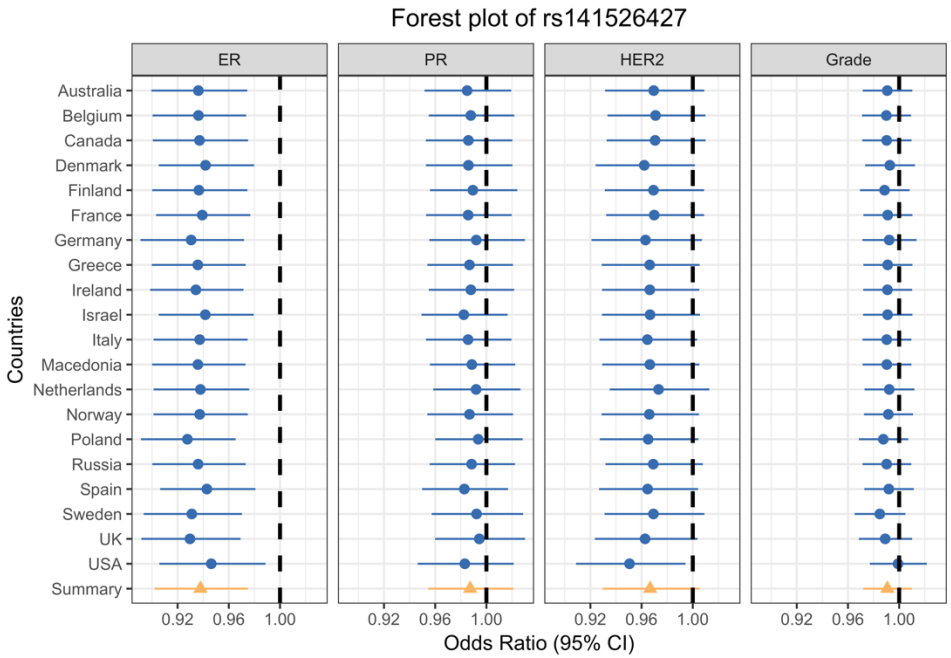


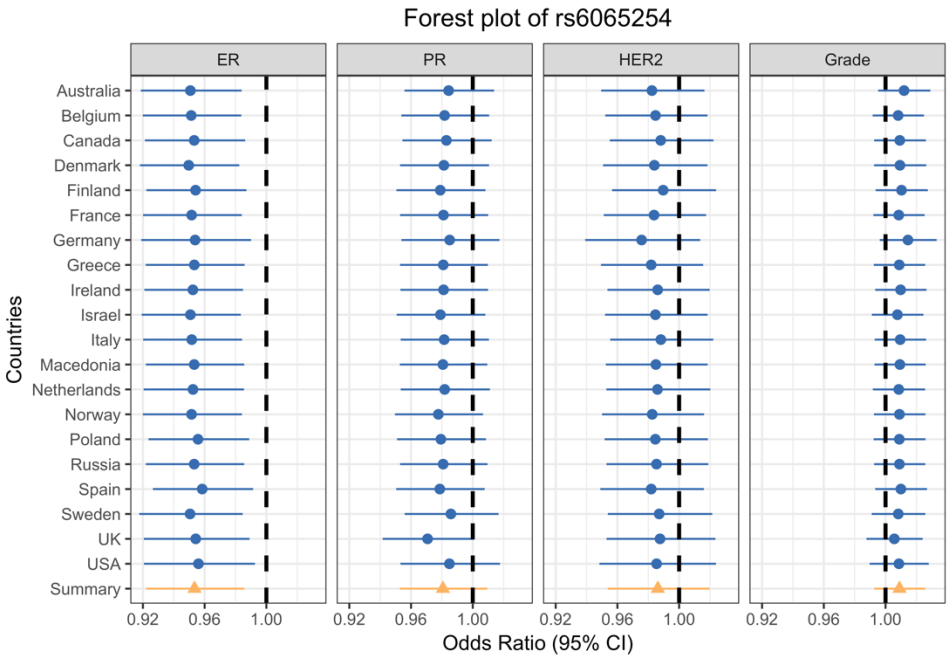
Supplementary figure 5 continued. Regional plots of the 32 identified breast cancer variants. The first 22 variants were identified through standard logistic regression (n = 133,384 cases, n = 113,789 controls), the following eight variants were identified through two-stage polytomous regression (n = 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 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
ER
PR
HER2
Grade
Australia
Belgium
Canada
Denmark
Finland
France
Germany
Greece
Ireland
Israel
Italy
Macedonia
Netherlands
Norway
Poland
Russia
Spain
Sweden
UK
USA
Summary
Countries
0.92
0.96
1.00
Odds Ratio (95% CI)


Forest plot of rs6065254
ER
PR
HER2
Grade
Australia
Belgium
Canada
Denmark
Finland
France
Germany
Greece
Ireland
Israel
Italy
Macedonia
Netherlands
Norway
Poland
Russia
Spain
Sweden
UK
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Summary
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0.92
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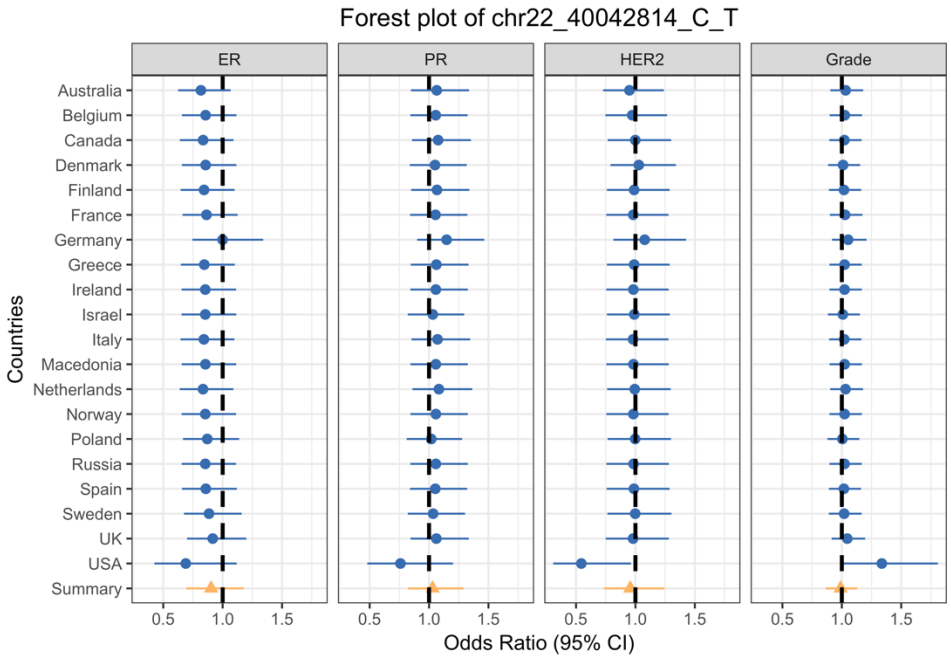
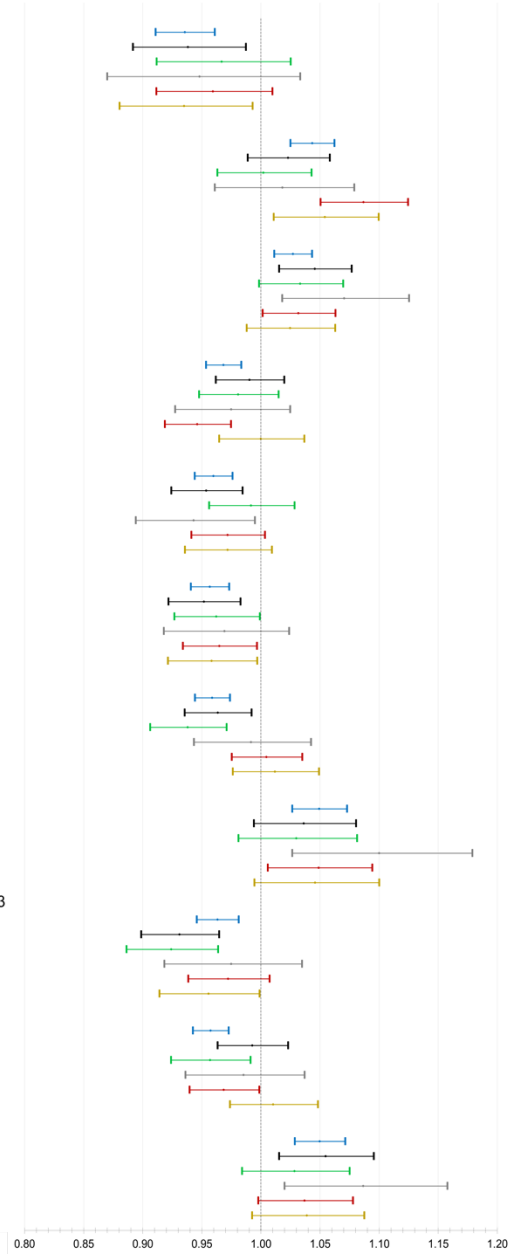
Odds Ratio (95% CI)


Forest plot of chr22_40042814_C_T
ER
PR
HER2
Grade
Australia
Belgium
Canada
Denmark
Finland
France
Germany
Greece
Ireland
Israel
Italy
Macedonia
Netherlands
Norway
Poland
Russia
Spain
Sweden
UK
USA
Summary
Countries
0.5
1.0
1.5
Odds Ratio (95% CI)

Supplementary Figure 7. Associations[1] between novel susceptibility variants identified using standard logistic regression with intrinsic-like breast cancer subtypes[2] (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).

				Global etiologic	Tumor characteristic heterogeneity *P*[4]			
rs5776993	1	110,222,901	0.12	0.50	0.29	0.54	0.35	0.29
rs9712235	2	67,881,757	0.26	6.70E-03	3.68E-04	0.02	0.03	0.85
rs4602255	2	69,392,128	0.45	0.17	0.69	0.67	0.62	0.11
rs1375631	3	16,778,867	0.5	0.40	0.09	0.21	0.57	0.55
rs2886671	3	59,373,745	0.43	0.67	0.75	0.52	0.43	0.39
rs34052812	3	156,535,958	0.33	0.98	0.74	0.72	0.62	0.97
rs7760611	6	21,903,533	0.47	1.40E-03	0.03	0.28	0.17	0.87
rs188092014	7	74,341,926	0.19	0.19	0.05	0.30	0.78	0.19
rs79518236	7	98,026,554	0.23	1.57E-03	0.37	0.02	0.30	1.94E-03
rs142890050	8	23,480,253	0.46	0.48	0.60	0.69	0.91	0.26
rs13256025	8	25,831,778	0.2	0.69	0.32	0.59	0.81	0.80



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-)

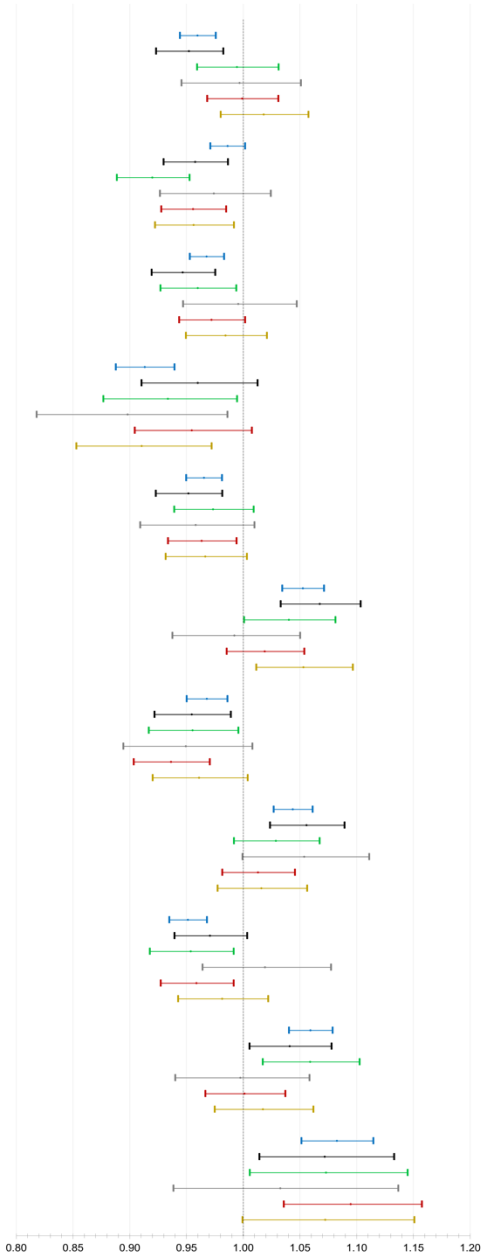
3. Based on a mixed-effect two-stage polytomous model testing for heterogeneity between susceptibility variants and ER, PR, HER2, and grade, where ER was entered into the model as a fixed-effect term and PR, HER2, and grade were entered into the model as random-effect terms.

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. Associations[1] between novel susceptibility variants identified using standard logistic regression with intrinsic-like breast cancer subtypes[2] (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).

				Global etiologic	Tumor characteristic heterogeneity *P*[4]			
rs13277568	8	116,679,547	0.37	0.06	0.90	0.19	0.17	0.34
rs4742903	9	106,856,793	0.44	2.80E-03	0.34	0.37	0.05	0.01
rs10838267	11	44,368,892	0.45	0.85	0.39	0.54	0.69	0.81
12:29140260	12	29,140,260	0.09	0.39	0.31	0.63	0.67	0.37
rs11065822	12	111,600,134	0.37	0.87	0.52	0.70	0.69	0.78
rs1061657	12	115,108,136	0.26	0.04	0.07	0.45	0.35	0.38
rs11652463	17	70,405,095	0.31	0.21	0.63	0.17	0.90	0.92
rs12962334	18	20,477,934	0.32	0.06	0.02	0.28	0.70	0.15
rs17743054	18	42,900,892	0.28	2.40E-06	0.04	0.25	0.01	0.01
rs13039563	20	52,296,849	0.24	4.88E-03	0.14	0.26	0.81	0.44
rs9808759	21	47,780,223	0.07	0.71	0.50	0.29	0.44	0.29



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-)

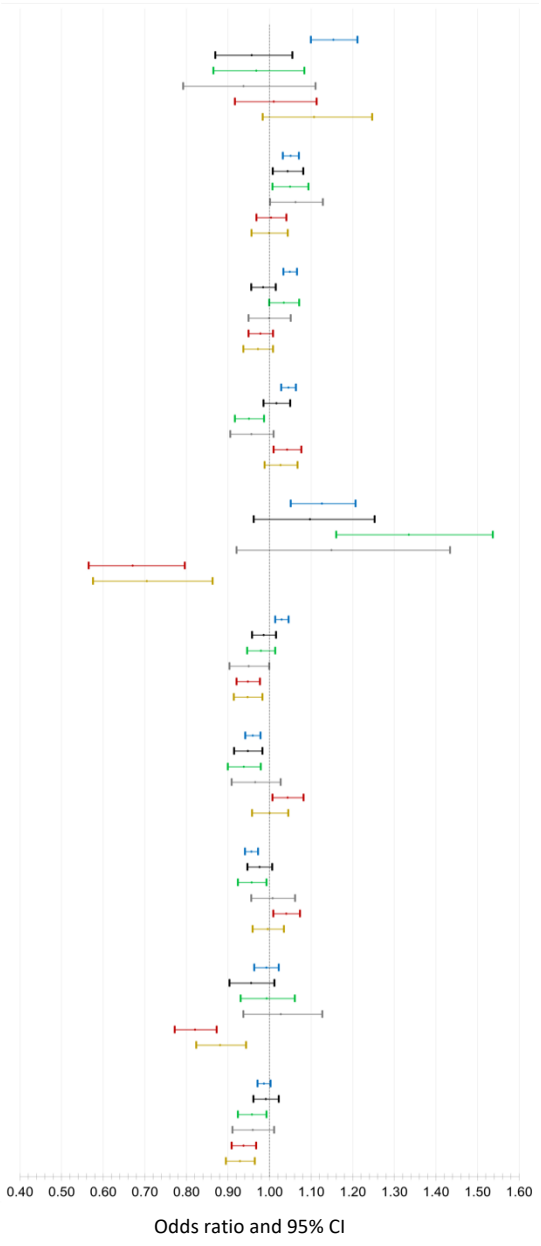
3. Based on a mixed-effect two-stage polytomous model testing for heterogeneity between susceptibility variants and ER, PR, HER2, and grade, where ER was entered into the model as a fixed-effect term and PR, HER2, and grade were entered into the model as random-effect terms.

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 8 Risk[1] of breast cancer subtypes defined by intrinsic-like subtypes[2] (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.

Variant	chromosome	Position	MAF	Global etiologic heterogeneity *P*[3]	Tumor characteristic heterogeneity *P*[4]			
					ER[5]	PR[5]	HER2[5]	grade
chr1:145126177	1	145,126,177	0.04	2.8E-06	5.04E-01	5.35E-02	1.18E-01	6.87E-04
rs495367	4	1,986,972	0.35	5.8E-02	1.35E-01	9.22E-01	3.09E-01	2.42E-01
chr5:67424121	5	67,424,121	0.45	5.2E-07	1.70E-01	1.31E-01	4.20E-01	2.79E-03
rs7924772	11	120,233,626	0.39	1.4E-03	6.69E-01	8.31E-01	1.41E-06	9.95E-02
rs78378222	17	7,571,752	0.01	9.1E-08	7.01E-06	8.96E-01	2.67E-04	5.15E-01
rs206435	18	10,354,649	0.5	1.1E-09	2.79E-03	2.51E-01	1.44E-01	2.83E-04
rs141526427	20	11,502,618	0.25	6.2E-05	1.26E-03	4.44E-01	8.88E-02	3.22E-01
rs6065254	20	39,248,265	0.39	7.3E-07	4.34E-03	1.98E-01	3.92E-01	2.74E-01
rs17215231	6	33,239,869	0.08	2.4E-06	4.40E-02	2.46E-01	9.12E-03	7.87E-03
rs2464195	12	121,435,475	0.37	1.0E-02	8.92E-02	9.99E-01	4.05E-01	3.41E-01



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-)

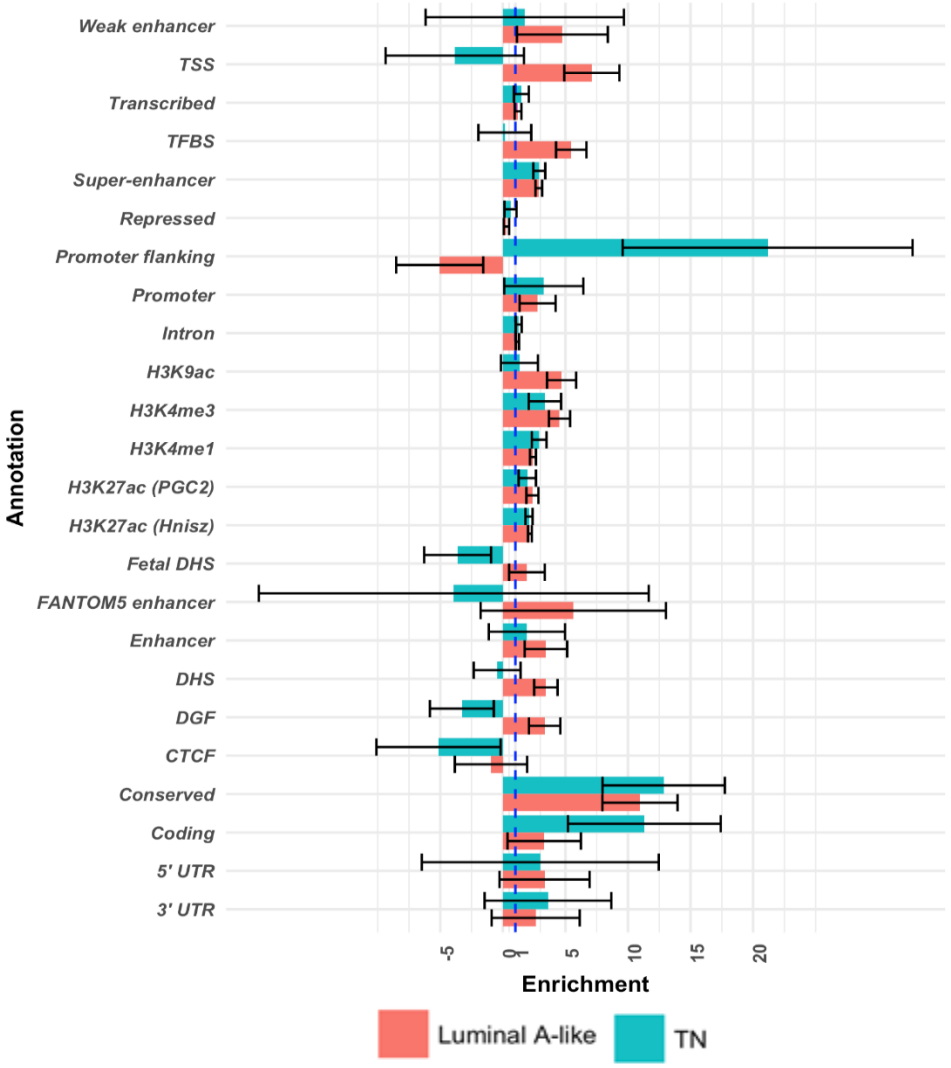
3. Based on a mixed-effect two-stage polytomous model testing for heterogeneity between susceptibility variants and ER, PR, HER2, and grade, where ER was entered into the model as a fixed-effect term and PR, HER2, and grade were entered into the model as random-effect terms.

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

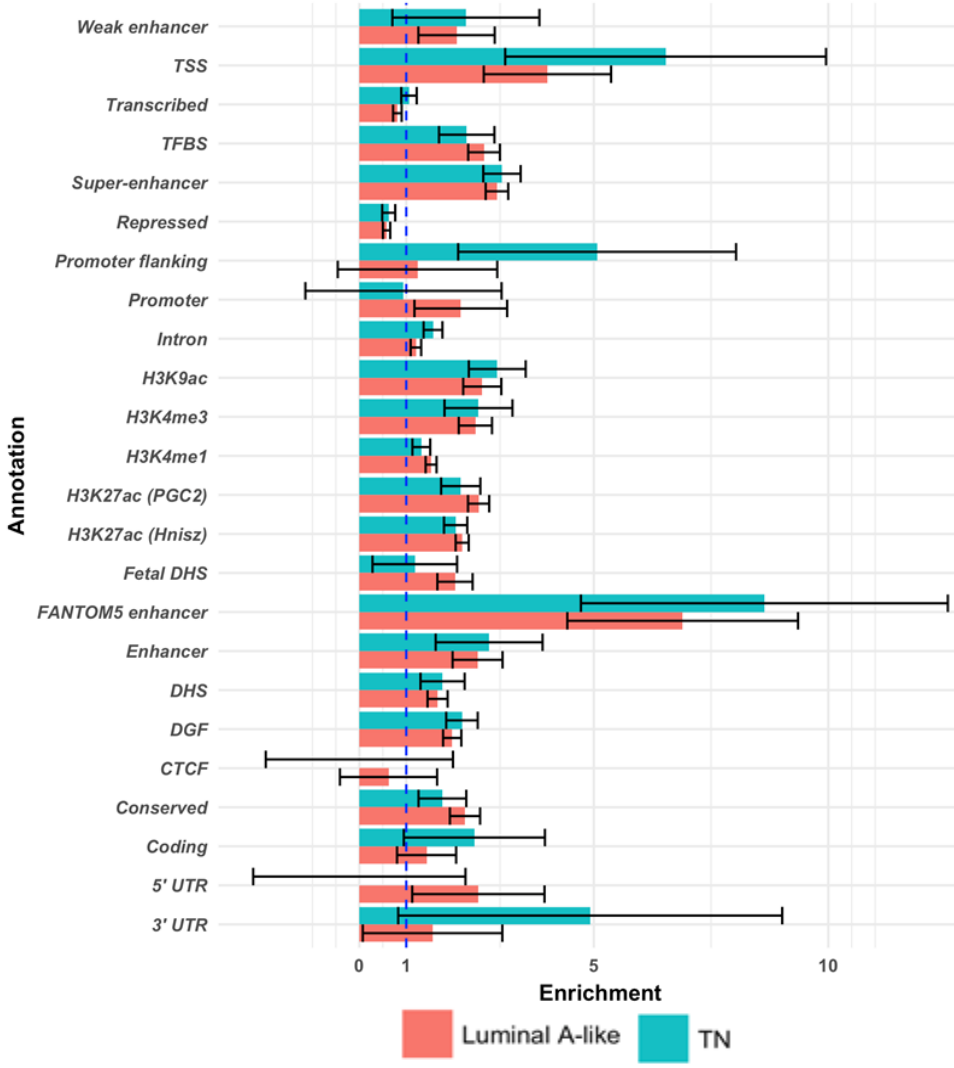
5. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2)

Supplementary figure 9. **a)** Enrichment analysis[1] results for 24 non-cell-type-specific, publicly available annotations for luminal A-like subtypes and triple-negative subtypes (n = 45,253 effective luminal A-like cases, n = 8,602 effective triple-negative cases, n = 91,477 controls). **b)** Enrichment analysis[1] results for 24 main annotations with ±500 bp extension for luminal A-like subtypes and triple-negative subtypes. No significant differences were found between luminal A-like and triple-negative after adjusting for multiple testing.

a)



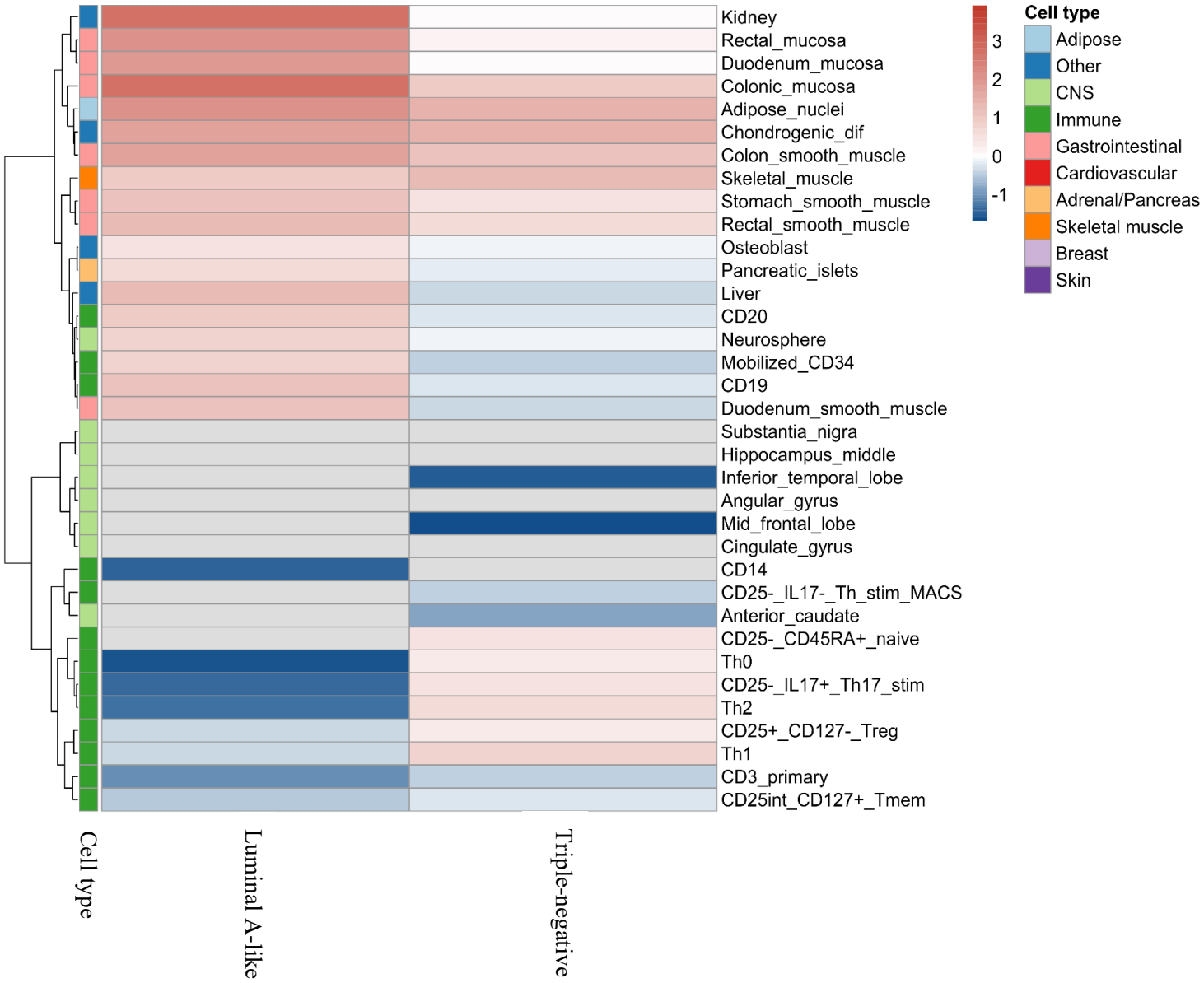
b)



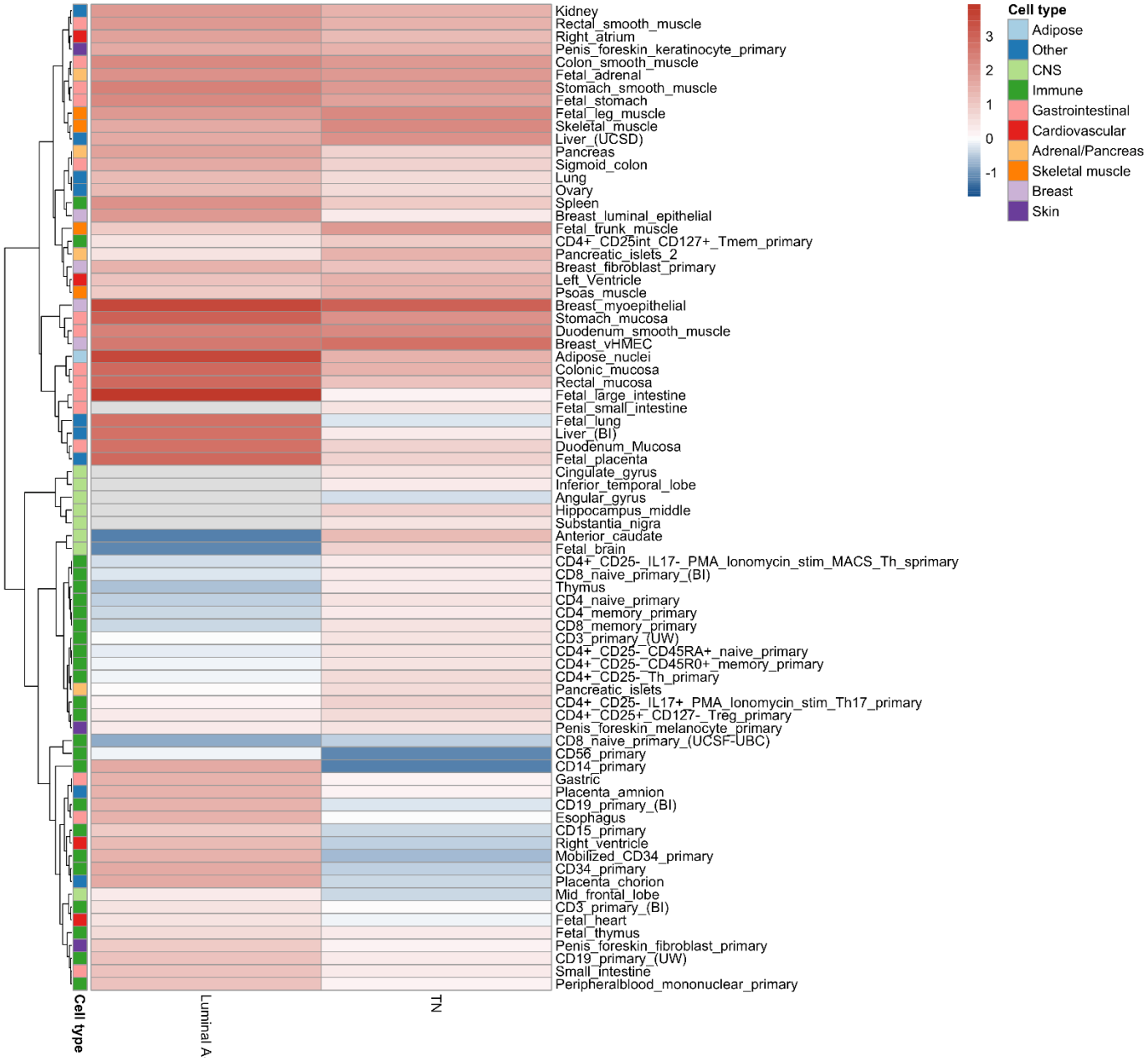
[1] Error bars represent Jackknife standard errors around the estimates of enrichment.

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 subtypes. Both luminal A-like and triple-negative subtypes were enriched for gastrointestinal cell types and suppression of central nervous system cells.

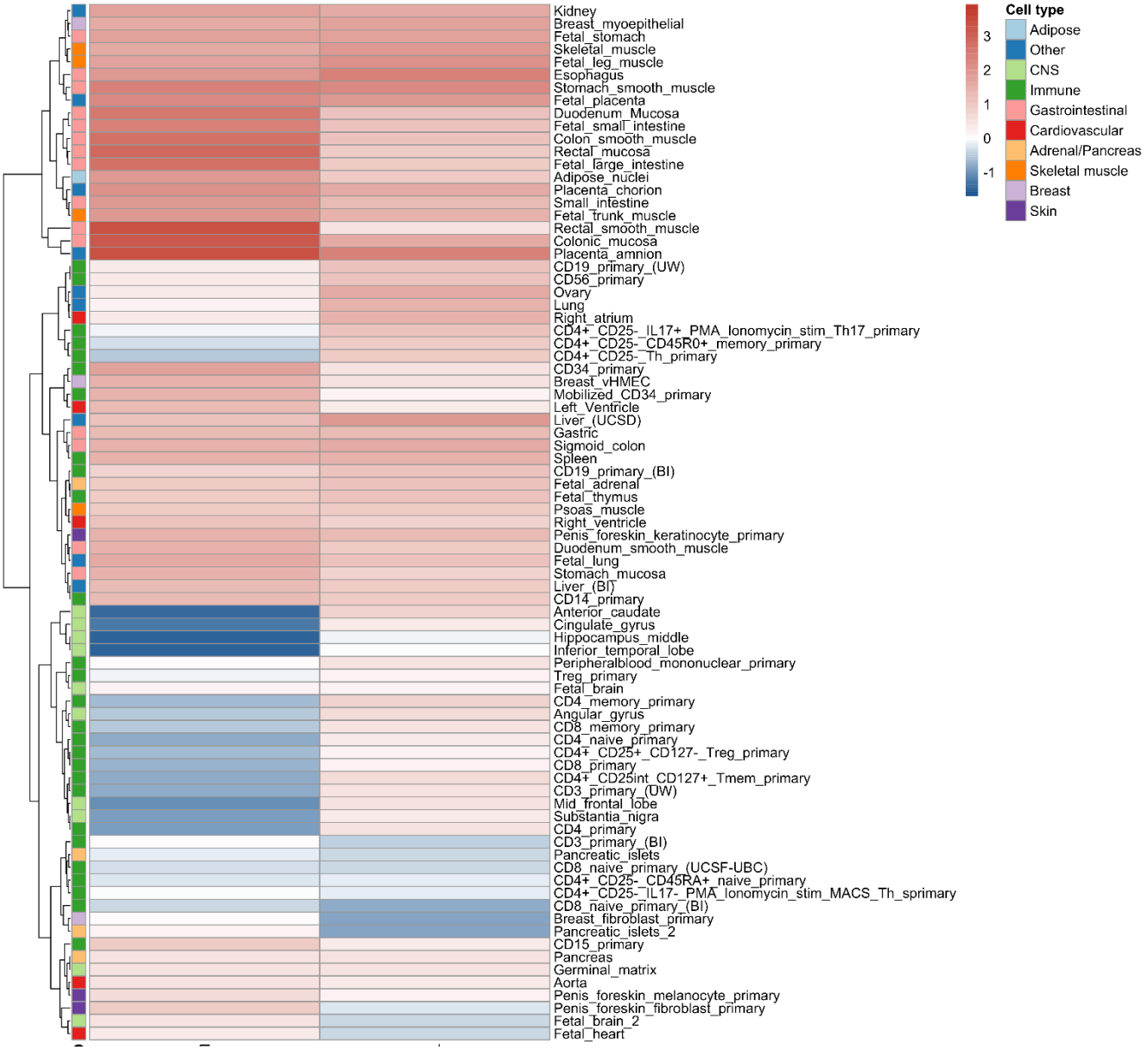
a) Heatmap showing patterns of cell-type specific enrichment for histone marks H3K27ac in luminal A-like tumors and TN tumors



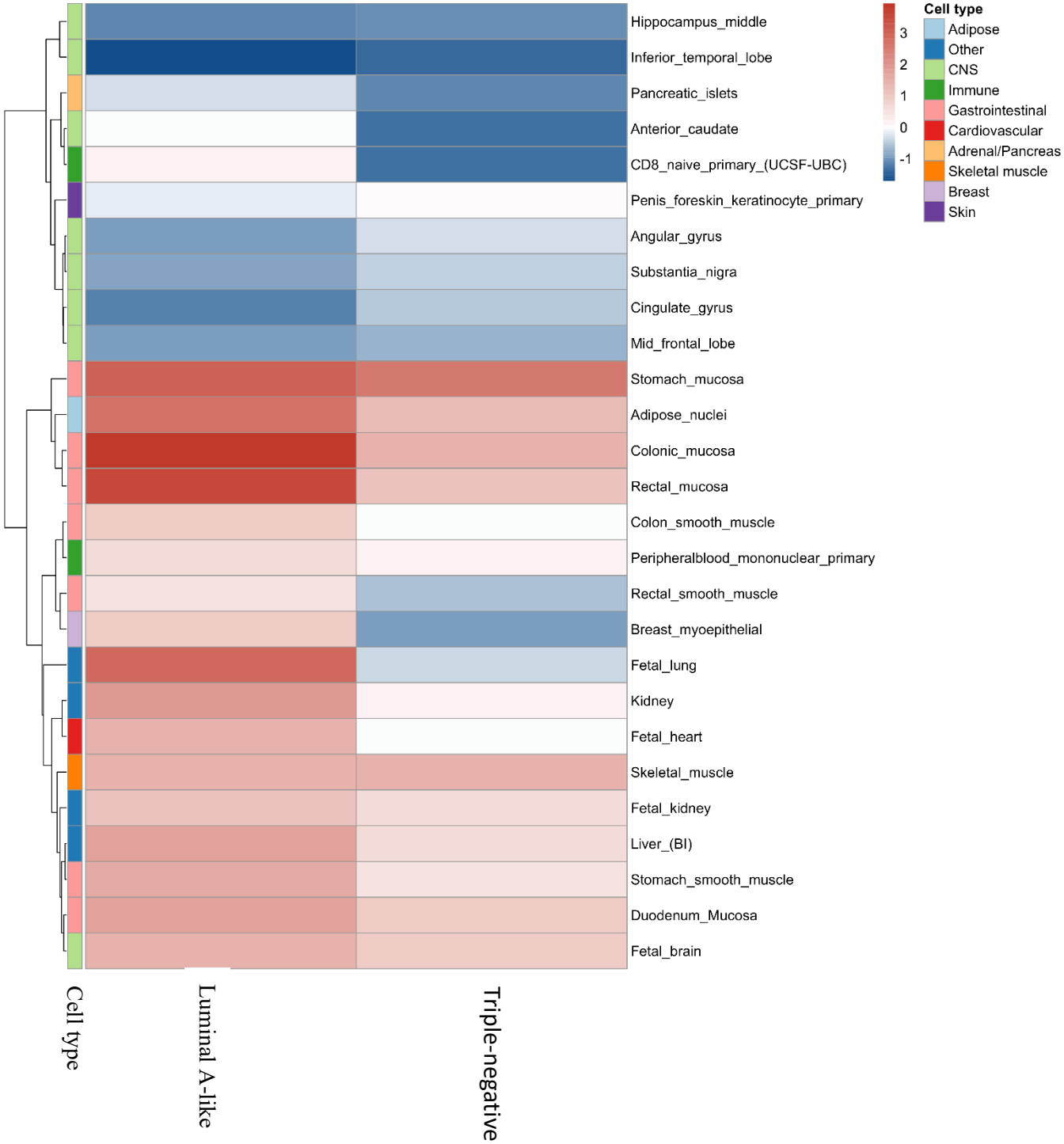
b) Heatmap showing patterns of cell-type specific enrichment for histone marks H3K4me1 in luminal A-like tumors and triple-negative tumors



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



d) Heatmap showing patterns of cell-type specific enrichment for histone marks H3K9ac in luminal A-like tumors and triple-negative 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 described[2]. Tumor tissue copy number was estimated from the Affymetrix 6.0 and called using the GISTIC2 algorithm[3]. 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 Consortium[4]. 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 ±2Mb 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 described[5]. eQTL analyses were performed using the MatrixEQTL program in R[6].

INQUISIT target gene analysis

Logic underlying INQUISIT predictions: Details of the INQUISIT pipeline have been previously described[1]. 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 HMECs[8]. We used breast cell line computational enhancer–promoter correlations (PreSTIGE[9], IM-PET[10], FANTOM5[11]) breast cell super-enhancer[12], breast tissue-specific expression variants (eQTL) from multiple independent studies (TCGA (normal

breast and breast tumor) and GTEx breast, **See eQTL Methods**), transcription factor and histone modification chromatin immunoprecipitation followed by sequencing (ChIP-seq) from the ENCODE and Roadmap Epigenomics Projects together with the genomic features found to be significantly enriched for all known breast cancer CCVs[13], gene expression RNA-seq from several breast cancer lines and normal samples (ENCODE) and topologically associated domain (TAD) boundaries from T47D cells (ENCODE[14]). To assess the impact of intragenic variants, we evaluated their potential to alter primary protein coding sequence and splicing using Ensembl Variant Effect Predictor[15] using MaxEntScan and dbscSNV 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 enriched[20] 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 analyses[16-18] as previously described[2] 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 R2>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 data [19]. 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 = 2x2x2). Let N denote the total sample size and let $\mathrm{D_i}$ denote the disease status of ith subject which can take values from $\{0,1,2,\dots,8\}$ and $\mathrm{i} = 1,2,\dots,\mathrm{N}$. $\mathrm{D_i} = 0$ represent a control, and $\mathrm{D_i} = m$ represent the ith subject with the breast cancer subtypes M. Let $\mathrm{G_i}$ denote the genotype of a variant for ith subject, taking values from $\{0,1,2\}$. Let $\mathbf{X_i}$ denote the other covariates for the ith subject, for example principal components or age. In the first stage of the model, we fit a standard “saturated” polytomous logistic regression model:

$$\Pr(\mathrm{D_i} = \mathrm{m}|\mathrm{G_i}, \mathrm{X_i}) = \frac{\exp(\beta_m G_i + \boldsymbol{\eta_m^T X_i})}{1 + \sum_{m=1}^{8} \exp(\beta_m G_i + \boldsymbol{\eta_m^T X_i})}, \quad (1)$$

where β_{m} is the regression coefficient for a variant (G) associated with the mth subtype and η_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:

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

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. $\theta_{\mathrm{k}}^{(1)}$ represents the case-case log odds ratio for the kth tumor characteristic after adjusting for the other tumor characteristics. We also refer $\theta_{\mathrm{k}}^{(1)}$ as the main effect of the kth tumor characteristic. $\theta_{\mathrm{k_1 k_2}}^{(2)}$ represents how the case-case log odds ratio associated with k_1th tumor characteristic is modified by levels of the k_2th tumor characteristic and vice versa. We also refer to $\theta_{\mathrm{k_1 k_2}}^{(2)}$ as the pairwise interaction between the k_1th tumor characteristic and the k_2th 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:

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

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:

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

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:

$$H_0\colon \theta^{(0)}=0 \; and \; \boldsymbol{\theta^H}=\mathbf{0} \; versus \; H_1\colon either \; \theta^{(0)}\neq 0 \text{ or } \boldsymbol{\theta^H}\neq \mathbf{0}\,. \tag{8}$$

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:

$$H_0\colon \boldsymbol{\theta^H}=\mathbf{0} \; versus \; H_1\colon \boldsymbol{\theta^H}\neq \mathbf{0}\,. \tag{8}$$

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:

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

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 $H_0: \theta_1^{(1)} = 0 \; versus \; H_0: \theta_1^{(1)} \neq \; 0$. 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 heterogeneity [20]. 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:

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

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:

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

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 note 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 (ER-, PR-, HER2-). To estimate the case-control log odds ratios of these five intrinsic subtypes we can construct the two-stage model as:

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

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

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

where $\boldsymbol{\beta}^{(J)}=(\beta_1^{(J)},\beta_2^{(J)},\dots,\beta_M^{(J)})$ are the joint effect sizes. We define the heritability as $h^2=var(\left(\boldsymbol{\beta}^{(J)}\right)^T\boldsymbol{X})$, assuming X is standardized with mean 0 variance 1. If 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 jth variant. Therefore, the expected chi-square statistics (z_j^2) of variant j is

$$\mathrm{E}\left(z_j^2|l_j\right) = \frac{E\left(\hat{\beta}_j^2|l_j\right)}{s_j^2} = \frac{\left[E\left\{\left(\hat{\beta}_j - \beta_j\right)^2\middle|l_j\right\} + 2E\left[\left(\hat{\beta}_j - \beta_j\right)\beta_j|l_j\right] + E\left(\beta_j^2|l_j\right)\right]}{s_j^2} \tag{13}$$

$$= \frac{\left[E\left\{\left(\hat{\beta}_j - \beta_j\right)^2\middle|l_j\right\} + E\left(\beta_j^2|l_j\right)\right]}{s_j^2}$$

$$= 1 + \frac{E\{(\sum_k r_{jk}\beta_k^{(J)})^2\}}{s_j^2}$$

$$= 1 + \frac{h^2}{M}\frac{l_j}{s_j^2},$$

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:

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

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

$$\mathrm{E}\left(\mathrm{z_{1j}}z_{2j}|l_j\right) = \frac{E\left(\hat{\beta}_{1j}\,\hat{\beta}_{2j}|l_j\right)}{s_{1j}s_{2j}} \tag{15}$$

$$= \frac{\left[E\left\{\left(\hat{\beta}_{1j} - \beta_{1j}\right)\left(\hat{\beta}_{2j} - \beta_{2j}\right)|l_j\right\} + E\left(\beta_{1j}\beta_{2j}|l_j\right)\right]}{s_{1j}s_{2j}}$$

$$= \frac{s_{12j}}{s_{1j}s_{2j}} + \frac{E\left(\sum_k r_{jk}\beta_{1k}^{(J)}\sum_k r_{jk}\beta_{2k}^{(J)}\,|l_j\right)}{s_{1j}s_{2j}}$$

$$= \frac{s_{12j}}{s_{1j}s_{2j}} + \frac{\rho_g}{M}\frac{l_j}{s_{1j}s_{2j}},$$

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

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

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 kth subtype and n_0 for the control. If we fit a two-stage polytomous model for the jth variant, the corresponding log odds ratio for kth subtype is $\hat{\beta}_{jk}$ and the standard error is s_{jk}. Then, approximately:

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

where p_j is the MAF of the jth 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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