

Fine-mapping of 150 breast cancer risk regions identifies 178 high confidence target genes

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ABSTRACT

Genome-wide association studies have identified breast cancer risk variants in over 150 genomic regions, but the mechanisms underlying risk remain largely unknown. These regions were explored by combining association analysis with *in silico* genomic feature annotations. We defined 205 independent risk-associated signals with the set of credible causal variants (CCVs) in each one. In parallel, we used a Bayesian approach (PAINTOR) that combines genetic association, linkage disequilibrium, and enriched genomic features to determine variants with high posterior probabilities (HPPs) of being causal. Potentially causal variants were significantly over-represented in active gene regulatory regions and transcription factor binding sites. We applied our INQUSIT pipeline for prioritizing genes as targets of potentially causal variants, using gene expression (eQTL), chromatin interaction and functional annotations. Known cancer drivers, transcription factors and genes in the developmental, apoptosis, immune system and DNA integrity checkpoint gene ontology pathways, were over-represented among the 178 highest confidence target genes.

INTRODUCTION

Genome-wide association studies (GWAS) have identified genetic variants associated with breast cancer risk in more than 150 genomic regions^{1,2}. However, the variants and genes driving these associations are mostly unknown, with fewer than 20 regions studied in detail³⁻²⁰. Here, we aimed to fine-map all known breast cancer susceptibility regions using dense genotype data on > 217K subjects participating in the Breast Cancer Association Consortium (BCAC) and the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA). All samples were genotyped using the OncoArrayTM^{1,2,21} or the iCOGS chip^{22,23}. Stepwise multinomial logistic regression was used to identify independent association signals in each region and define credible causal variants (CCVs) within each signal. We found genomic features significantly overlapping the CCVs and then used a Bayesian approach, integrating informative genomic features and genetic associations, to refine the set of likely causal variants and calculate their posterior probabilities. Finally, we integrated genetic and *in silico* epigenetic, expression and chromatin conformation data to infer the likely target genes of each signal.

RESULTS

Most breast cancer genomic regions contain multiple independent risk-associated signals

We included 109,900 breast cancer cases and 88,937 controls, all of European ancestry, from 75 studies in the BCAC. Genotypes (directly observed or imputed) were available for 639,118 single nucleotide polymorphisms (SNPs), deletion/insertions, and copy number variants (CNVs) with minor allele frequency (MAF) $\geq 0.1\%$ within 152, previously defined, risk-associated regions (**Supplementary Table 1; Figure 1**). Multivariate logistic regression confirmed associations for 150/152 regions at a p-value $< 10^{-4}$ significance threshold (**Supplementary Table 2A**). To determine the number of independent risk

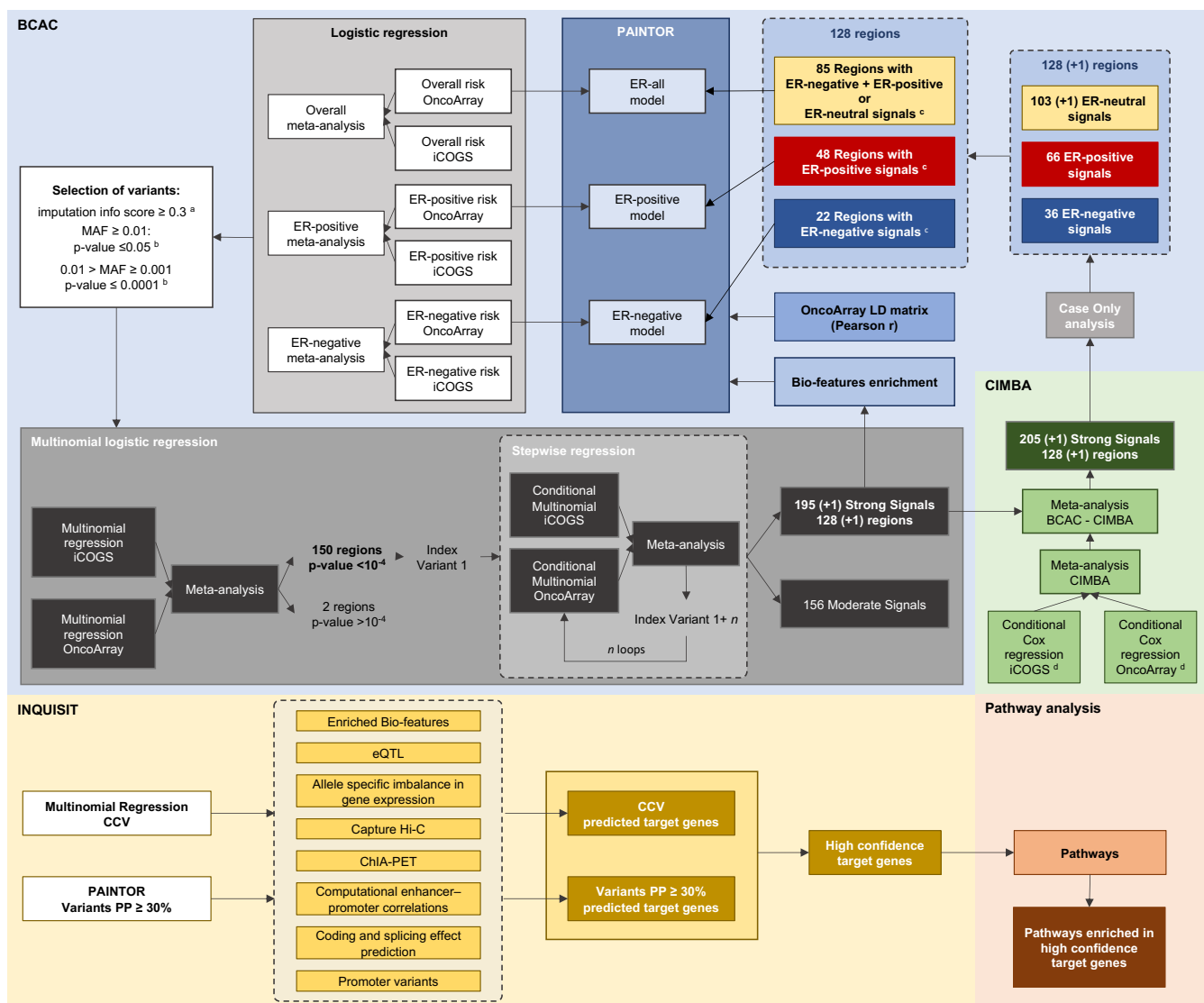


Figure 1. Flowchart summarizing the study design. ^a In iCOGS and in OncoArray; ^b for at least one phenotype; ^c regions containing signals associated with more than one phenotype were evaluated with more than one PAINTOR model; ^d conditional on the index variants from BCAC strong signals.

signals within each region we applied stepwise multinomial logistic regression, deriving the association of each variant, conditional on the more significant ones, in order of statistical significance. Finally, we defined CCVs in each signal as variants with conditional p-values within two orders of magnitude of the

index variant ²⁴. We classified the evidence for each independent signal, and its CCVs, as either *strong* (conditional p-values $<10^{-6}$) or *moderate* ($10^{-6} < \text{conditional p-values} < 10^{-4}$).

From the 150 genomic regions we identified 352 independent risk signals containing 13,367 CCVs, 7,394 of these were within the 196 strong-evidence signals across 129 regions (**Figures 2A-B**). The number of signals per region ranged from 1 to 9, with 79 (53%) containing multiple signals. We noted a wide range of CCVs per signal, but in 42 signals there was only a single CCV and this was assumed to be causal (**Figures 2C-D, Table 1**).

The majority of breast tumors express the estrogen receptor (ER-positive), but ~20% do not (ER-negative); these two tumor types have distinct biological and clinical characteristics ²⁵. Using a case-only analysis for the 196 strong-evidence signals, we found 66 signals (34%; containing 1,238 CCVs) where the lead variant conferred a greater relative-risk of developing ER-positive tumors (false discovery rate, FDR 5%), and 29 (15%; 646 CCVs) where the lead variant conferred a greater risk of ER-negative cancer tumors (FDR 5%) (**Supplementary Table 2B, Figure 2E**). The remaining 101 signals (51%, 5,510 CCVs) showed no difference by ER status (referred to as ER-neutral).

Patients with *BRCA1* mutations are more likely to develop ER-negative tumors ²⁶. Hence, to increase our power to identify ER-negative signals, we performed a fixed-effects meta-analysis, combining association results from *BRCA1* mutation carriers in CIMBA with the BCAC ER-negative association results. This meta-analysis identified ten additional signals, seven ER-negative and three ER-neutral,

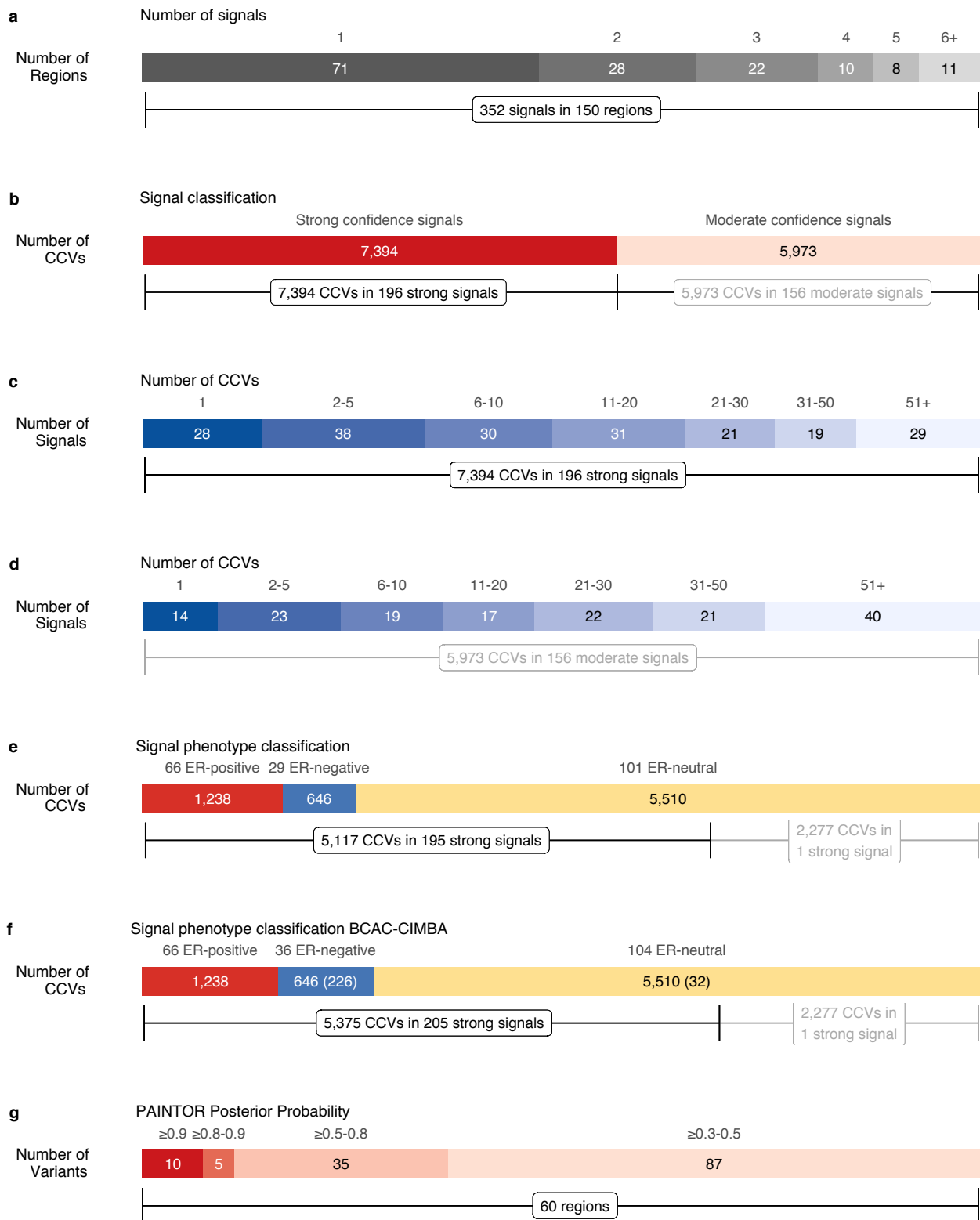


Figure 2. Determining independent risk signals and credible candidate variants (CCVs). (a) Number of independent signals per region identified through multinomial stepwise logistic regression. (b) Signal classification according to their confidence into strong and moderate confidence signals. (c) Number of CCVs per signal at strong confidence signals identified through multinomial stepwise logistic regression. (d) Number of CCVs per signal at moderate confidence signals identified through multinomial stepwise regression. (e) Subtype classification of strong signals into ER-positive, ER-negative and signals equally associated with both phenotypes (ER-neutral) from BCAC analysis. (f) Subtype classification from the meta-analysis of BCAC and CIMBA. Between brackets, number of CCVs from the meta-analysis of BCAC and CIMBA. (g) Number of variants at different posterior probability thresholds. 15 variants reach a PP $\geq 80\%$ by at least one of the three models (ER-all, ER-positive, ER-negative).

making 206 strong-evidence signals (17% ER-negative) containing 7,652 CCVs in total (**Figure 2F**). More than one quarter of the CCVs (2,277) were accounted for by one signal, resulting from strong linkage disequilibrium with a copy number variant. The remaining analyses focused on the other 205 strong signals across 128 regions (**Supplementary Table 2C**).

CCVs are over-represented in active gene-regulatory regions and transcription factor binding sites (TFBSs)

We constructed a database of mapped genomic-features in seven primary cells derived from normal breast and 19 breast cell lines using publicly available data, resulting in 811 annotation tracks in total. These ranged from general features, such as whether a variant was in an exon or in open chromatin, to more specific features, such a cell-specific TF binding or histone mark (determined through ChIP-Seq experiments) in breast-derived cells or cell lines. Using logistic regression, we examined the overlap of these genomic-features with the positions of 5,117 CCVs in the 195 strong-evidence BCAC signals versus the positions of 622,903 variants excluded as credible candidates in the same regions (**Supplementary**

Figure 1A, Supplementary Table 3). We found significant enrichment of CCVs (FDR 5%) in the following genomic-features:

(i) Open chromatin (determined by DNase-seq and FAIRE-seq) in ER-positive breast cancer cell-lines and normal breast (**Figure 3A**). Conversely, we found depletion of CCVs within heterochromatin (determined by the H3K9me3 mark in normal breast, and by chromatin-state in ER-positive cells ²⁷).

(ii) Actively transcribed genes in normal breast and ER-positive cell lines (defined by H3K36me3 or H3K79me2 histone marks, **Figure 3A**). Enrichment was larger for ER-neutral CCVs than for those affecting either ER-positive or ER-negative tumors.

(iii) Gene regulatory regions. CCVs overlapped distal gene regulatory elements in ER-positive breast cancer cells lines (defined by H3K4me1 or H3K27ac marks, **Figure 3B**). This was confirmed using the ENCODE definition of active enhancers in MCF-7 cells (enhancer-like regions defined by combining DNase and H3K27ac marks), as well as the definition of ²⁸ and ²⁷ (Supplementary Table 3). Under these more stringent definitions, enrichment among ER-positive CCVs was significantly larger than ER-negative or ER-neutral CCVs. Data from ²⁷, showed that 73% of active enhancer regions overlapped by ER-positive CCVs in ER-positive cells (MCF-7), are inactive in the normal HMEC breast cell line; thus, these enhancers appear to be MCF-7-specific.

We also detected significant enrichment of CCVs in active promoters in ER-positive cells (defined by H3K4me3 marks in T-47D), although the evidence for this effect was weaker than for distal regulatory elements (defined by H3K27ac marks in MCF-7, **Figure 3B**). Only ER-positive CCVs were significantly

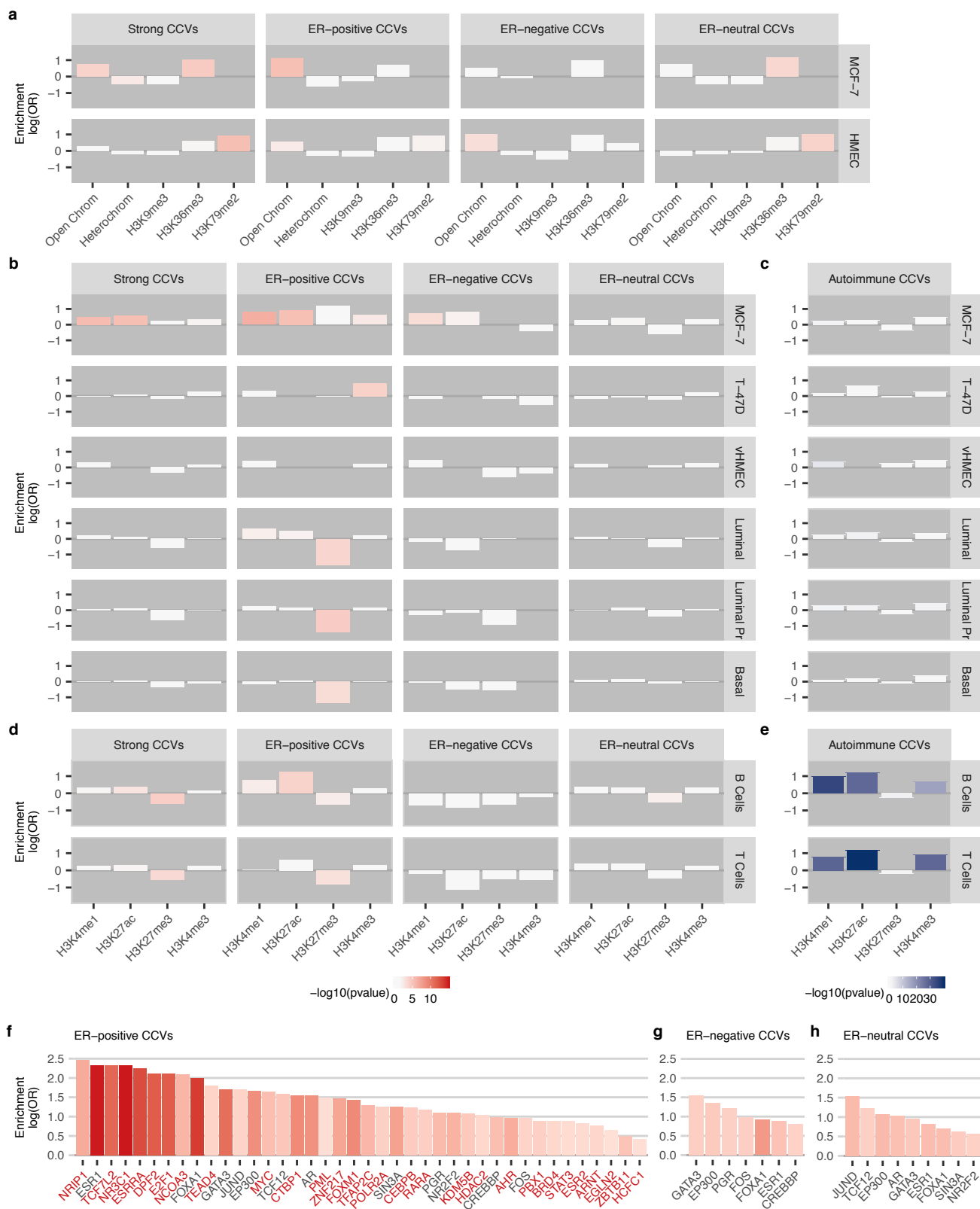


Figure 3. Overlap of CCVs with gene regulatory regions gene bodies and transcription factor binding sites. (a) Breast cancer CCVs overlap with chromatin states and broad breast cells epigenetic marks. (b) Breast cancer CCVs overlap with breast cells epigenetic marks. (c) Autoimmune CCVs overlap with breast cells epigenetic marks. (d) Breast cancer CCVs overlap with autoimmune-related epigenetic marks. (e) Autoimmune CCVs overlap with autoimmune-related epigenetic marks. (f) Significant ER-positive CCVs overlap with transcription factors binding sites. TFBSs found significant for ER-positive CCVs are highlighted in red (x axis labels). (g) Significant ER-negative CCVs overlap with transcription factors binding sites. (h) Significant ER-neutral CCVs overlap with transcription factors binding sites. Strong column: analysis with all CCVs at strong signals. ER-positive, ER-negative, ER-neutral: analysis of CCVs at strong signals stratified by phenotype.

enriched in T-47D active promoters. Conversely, CCVs were depleted among repressed gene-regulatory elements (defined by H3K27me3 marks) in normal breast (**Figure 3B**). As a control, we performed similar analyses with autoimmune disease CCVs ²⁹ (Methods) and relevant B and T cells (**Figures 3B-E**). The strongest evidence of enrichment of breast cancer CCVs was found at regulatory regions active in ER-positive cells (**Figure 3B**), whereas enrichment of autoimmune CCVs was in regulatory regions active in B and T cells (**Figure 3E**). We also compared the enrichment of our CCVs in enhancer-like and promoter-like regions (defined by ENCODE; **Supplementary Figure 1B**). The strongest evidence of enrichment of ER-positive CCVs in enhancer-like regions was found in MCF-7 cells, the only ER-positive cell line in ENCODE (**Supplementary Figure 1B**). These results highlight both the tissue- and disease-specificity of these histone marked gene regulatory regions.

(iv) We observed significant enrichment of CCVs in the binding sites for 40 TFBSs determined by ChIP-Seq (**Figures 3F-H**). The majority of the experiments were performed in ER-positive cell lines (90 TFBSs, 20 with data in ER-negative cell lines, 76 in ER-positive cell lines, and 16 in normal breast). These TFBSs

overlap each other and histone marks of active regulatory regions (**Supplementary Figure 2**). Enrichment in five TFBSs (ESR1, FOXA1, GATA3, TCF7L2, E2F1) has been previously reported ^{2,30}. All 40 TFBSs were significantly enriched in ER-positive CCVs (**Figure 3F**), seven were also enriched in ER-negative CCVs and nine in ER-neutral CCVs (**Figures 3G-H**). ESR1, FOXA1, GATA3 and EP300 TFBSs were enriched in all CCV ER-subtypes. However, the enrichment for ESR1, FOXA1 or GATA3 was stronger for ER-positive CCVs than for ER-negative or ER-neutral.

CCVs significantly overlap consensus transcription factor binding motifs

We investigated whether CCVs were also enriched within consensus TF binding motifs by conducting a motif-search within active regulatory regions (ER-positive CCVs at H3K4me1 marks in MCF-7). We identified 30 motifs, from eight TF families, with enrichment in ER-positive CCVs (FDR 10%, **Supplementary Table 4A**) and a further five motifs depleted among ER-positive CCVs. To assess whether the motifs appeared more frequently than by chance at active regulatory regions overlapped by our ER-positive CCVs, we compared motif-presence in a set of randomized control sequences (Methods). Thirteen of 30 motifs were more frequent at active regulatory regions with ER-positive CCV enrichment; these included seven homeodomain motifs and two fork head factors (**Supplementary Table 4B**).

When we looked at the change in predicted binding affinity, 57 ER-positive signals (86%) included at least one CCV predicted to modify the binding affinity of the enriched TFBSs (≥ 2 -fold, **Supplementary Table 4C**). Forty-eight ER-positive signals (73%) had at least one CCV predicted to modify the binding

affinity >10-fold. This analysis validates previous reports of breast cancer causal variants that alter DNA binding affinity for FOXA1^{3,30}

Bayesian fine -mapping incorporating functional annotations and linkage disequilibrium

As an alternative statistical approach, we applied PAINTOR³¹ to the same 128 regions (**Figure 1**). In brief, PAINTOR integrates genetic association results, linkage disequilibrium (LD) structure, and enriched genomic features in an empirical Bayes framework and derives the posterior probability (PP) of each variant being causal, conditional on available data. We identified seven variants with high posterior probability (HPP $\geq 80\%$) of being causal for all breast cancer types and ten for the ER-positive subtype (**Table 1**); two of these had HPP > 80% for both ER-positive and all breast cancer types. These 15 HPP variants (HPPVs; $\geq 80\%$) were distributed across 13 regions. We also identified an additional 35 variants in 25 regions with HPP ($\geq 50\%$ and < 80%) for ER-positive, ER-negative, or overall breast cancer (**Figure 2G**).

Consistent with the CCV analysis, we found evidence that most regions contained multiple HPPVs; the sum of PP across all variants in a region (an estimate of the number of distinct causal variants in the region) was > 2.0 for 84/86 regions analyzed for overall breast cancer, with a maximum of 16.1 and a mean of 6.4. For ER-positive cancer, 46/47 regions had total PP > 2.0 (maximum 18.3, mean 6.5) and for ER-negative, 17/23 regions had total PP > 2.0 (maximum 9.1, mean 3.2).

Although for many regions we were not able to identify HPP variants, we were able to reduce the proportion of variants needed to account for 80% of the total PP in a region to under 5% for 65 regions

for overall, 43 for ER-positive, and 18 for ER-negative breast cancer (**Figures S3A-C**). PAINTOR analyses were also able to reduce the set of likely causal variants in many cases. After summing the PPs for CCVs in each of the overall breast cancer signals, 39/100 strong-evidence signals had a total PP > 1.0. The number of CCVs in these signals ranged from 1 to 375 (median 24), but the number of variants needed to capture 95% of the total PP in each signal ranged from 1 to 115 (median 12), representing an average reduction of 43% in the number of variants needed to capture the signal.

PAINTOR and CCV analyses were generally consistent, yet complementary. Only 3.3% of variants outside of the set of strong-signal CCVs for overall breast cancer had PP > 1%, and only 48 (0.013%) of these had PP > 30% (**Supplementary Figure 3D**). At ER-positive and ER-negative signals respectively, 3.1% and 1.6% of the non-CCVs at strong signals had PP > 1%, and 40 (0.019%) and 3 (0.003%) of these had PP > 30% (**Figures S3E-F**). For the non-CCVs at strong-evidence signals with PP > 30%, the relatively high PP may be driven by the addition of functional annotation. The incorporation of functional annotation (relative to a PAINTOR model with no functional annotation) more than doubled PP for 64/88 variants.

CCVs co-localize with variants controlling local gene expression

We used four breast-specific expression quantitative trait loci (eQTL) data sets; to identify variants associated with differences in gene expression (eVariants): tumor tissue from the Nurses' Health Study (NHS) ³² and The Cancer Genome Atlas (TCGA) ³³, and normal breast tissue from the NHS and the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) ³⁴. We then examined the overlap of eVariants (defined as an eVariant within two orders of magnitude of the most significant

eVariant for a particular gene) with CCVs (Methods). There was significant overlap of CCVs with eVariants from both the NHS normal and breast cancer tissue studies (normal breast OR = 2.70, p-value = 1.7×10^{-5} ; tumor tissue OR = 2.34, p-value = 2.6×10^{-4} ; **Supplementary Table 3**). ER-neutral CCVs overlapped with eVariants in normal tissue more frequently than did ER-positive and ER-negative CCVs ($OR_{ER-neutral} = 3.51$, p-value = 1.3×10^{-5}). Cancer risk CCVs overlapped credible eVariants in 128/205 (62%) signals in at least one of the datasets (**Tables S5A-B**). Sixteen additional variants with PP $\geq 30\%$, not included among the CCVs, also overlapped with a credible eVariant (**Tables S5A-B**).

Transcription factors and known somatic breast cancer drivers are overrepresented among prioritized target genes

We assumed that causal variants function by affecting the behavior of a local target gene. However, it is challenging to define target genes or to determine how they may be affected by the causal variant. Few potentially causal variants directly affect protein coding: we observed 67/5,375 CCVs, and 19/137 HPPVs ($\geq 30\%$) in protein-coding regions. Of these, 33 (0.61%) were predicted to create a missense change, one a frameshift, and another a stop-gain, while 30 were synonymous (0.59%, **Supplementary Table 5C**). Four hundred and ninety-nine CCVs at 94 signals, and four additional HPPV ($\geq 30\%$), are predicted to create new splice sites or activate cryptic splice sites in 126 genes (**Supplementary Table 5D**). These results are consistent with previous observations that majority of common susceptibility variants are regulatory.

We applied an updated version of our pipeline INQUISIT - integrated expression quantitative trait and *in-silico* prediction of GWAS targets)² to prioritize potential target genes from 5,375 CCVs in strong

signals and all 138 HPPVs ($\geq 30\%$; **Supplementary Table 2C**). The pipeline predicted 1,204 target genes from 124/128 genomic regions examined. As a validation we examined the overlap between INQUISIT predictions and 278 established breast cancer driver genes³⁵⁻³⁹. Cancer driver genes were over-represented among high confidence (Level 1) targets; a 6-fold increase over expected from CCVs and 16-fold from HPPVs; $p\text{-value} = 1 \times 10^{-6}$; **Supplementary Figure 4A**). Notably, ten cancer driver genes (*CCND1*, *CHEK2*, *ESR1*, *FGFR2*, *GATA3*, *MAP3K1*, *MYC*, *TBX3*, *XPB1* and *ZFP36L1*) were predicted from the HPPVs derived from PAINTOR. Cancer driver gene status was consequently included as an additional weighting factor in the INQUISIT pipeline. TF genes⁴⁰ were also enriched amongst high-confidence targets predicted from both CCVs (2-fold, $p\text{-value} = 4 \times 10^{-4}$) and HPPVs (3-fold, $p\text{-value} = 7 \times 10^{-3}$, **Supplementary Figure 4A**).

In total INQUISIT prioritized 178 high-confidence target genes (**Table 2, Supplementary Table 6**). Significantly more genes were targeted by multiple independent signals ($N = 165$) than expected by chance ($p\text{-value} = 4.6 \times 10^{-8}$, **Supplementary Figure 4B, Figure 4A**). Six high-confidence predictions came only from HPPVs, although three of these (*IGFBP5*, *POMGNT1* and *WDYHV1*) had been predicted at lower confidence from CCVs. Target genes included 20 that were prioritized via potential coding/splicing changes (**Supplementary Table 7**), nine via promoter variants (**Supplementary Table 8**), and 166 via distal regulatory variants (**Supplementary Table 9**). We illustrate genes prioritized via multiple lines of evidence in **Figure 4A**.

Three examples of INQUISIT using genomic features to identify predict target genes. Based on capture Hi-C and ChIA-PET chromatin interaction data, *NR1P1* is a predicted target of intergenic CCVs and HPPVs

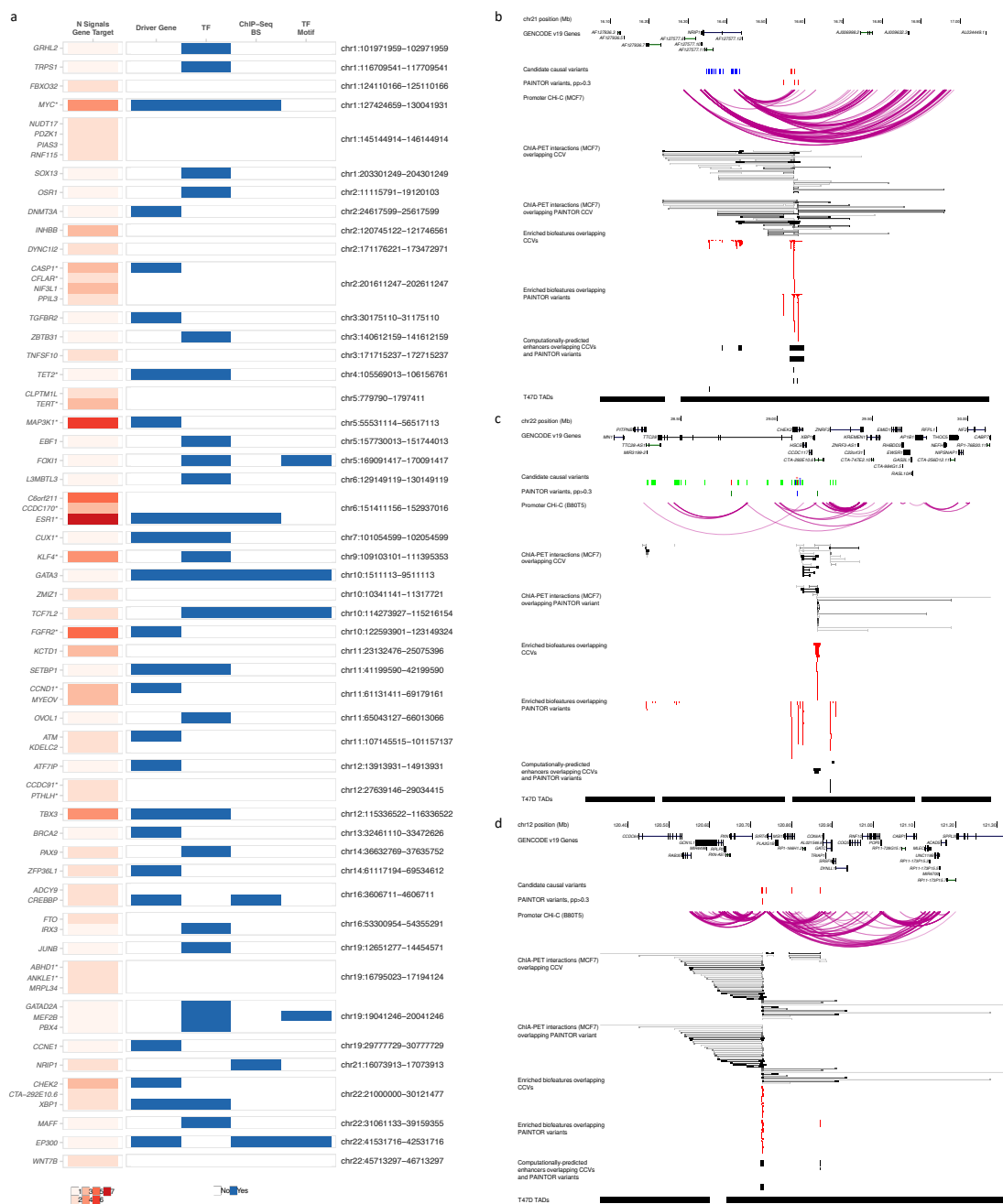


Figure 4. Predicted target genes are enriched in known breast cancer driver genes and transcription factors. (a) 79 target genes that fulfil at least one of the following criteria: are targeted by more than one independent signal, are known driver genes, transcription factor genes, or their binding sites (ChIP-Seq BS) or consensus motif (TF Motif) are significantly overlapped by CCVs. *Genes with published functional follow up. (b-d) In each panel, CCVs and PAINITOR variants with posterior probability >0.3 are shown, with independent signals in different colors. Chromatin interactions are shown as arcs (Capture Hi-C from selected breast cell lines) or boxes connected by lines, colored with gray-scale according to

interaction score (ENCODE ChIA-PET). Biofeatures which overlap CCVs from the global genomic enrichment analysis are depicted as red boxes. Computationally predicted enhancers including PreSTIGE, FANTOM5 and super-enhancers which overlap risk variants are represented by black boxes. High confidence INQUISIT target gene predictions include *NRIP1* (b), *CHEK2* and *XBP1* (c), and *RPLP0* and *MSI1* (d).

at chr21q21 (**Figure 4B**). Multiple target genes were predicted at chr22q12, including the driver genes *CHEK2* and *XBP1* (**Figure 4C**). A third example at chr12q24.31 is a more complicated scenario with two Level 1 targets: *RPLP0*⁴¹ and a modulator of mammary progenitor cell expansion, *MSI1*⁴² (Figure 4D).

Target gene pathways include DNA integrity-checkpoint, apoptosis, developmental processes and the immune system

We performed pathway analysis to identify common processes using INQUISIT high confidence target protein-coding genes (**Figure 5A**) and identified 457 Gene Ontology (GO) terms and 265 pathways at an FDR of 5% (**Supplementary Table 10**). These were grouped into 99 themes by common ancestor GO terms, pathways, or TF classes (**Figure 5B**). We found that 24% (14/58) of the ER-positive target genes were classified within developmental process pathways (including mammary development), 17% in immune system and a further 16% in cell differentiation pathways. Of genes targeted by ER-neutral signals, 19% (16/85) were classified in developmental process pathways, 18% in apoptotic process, and a further 16% in immune system pathways. The top themes of genes targeted by ER-negative signals were DNA integrity checkpoint (20%, 7/35), immune system, response to stimulus, and apoptotic processes, each containing 17% (6/35) of the genes.

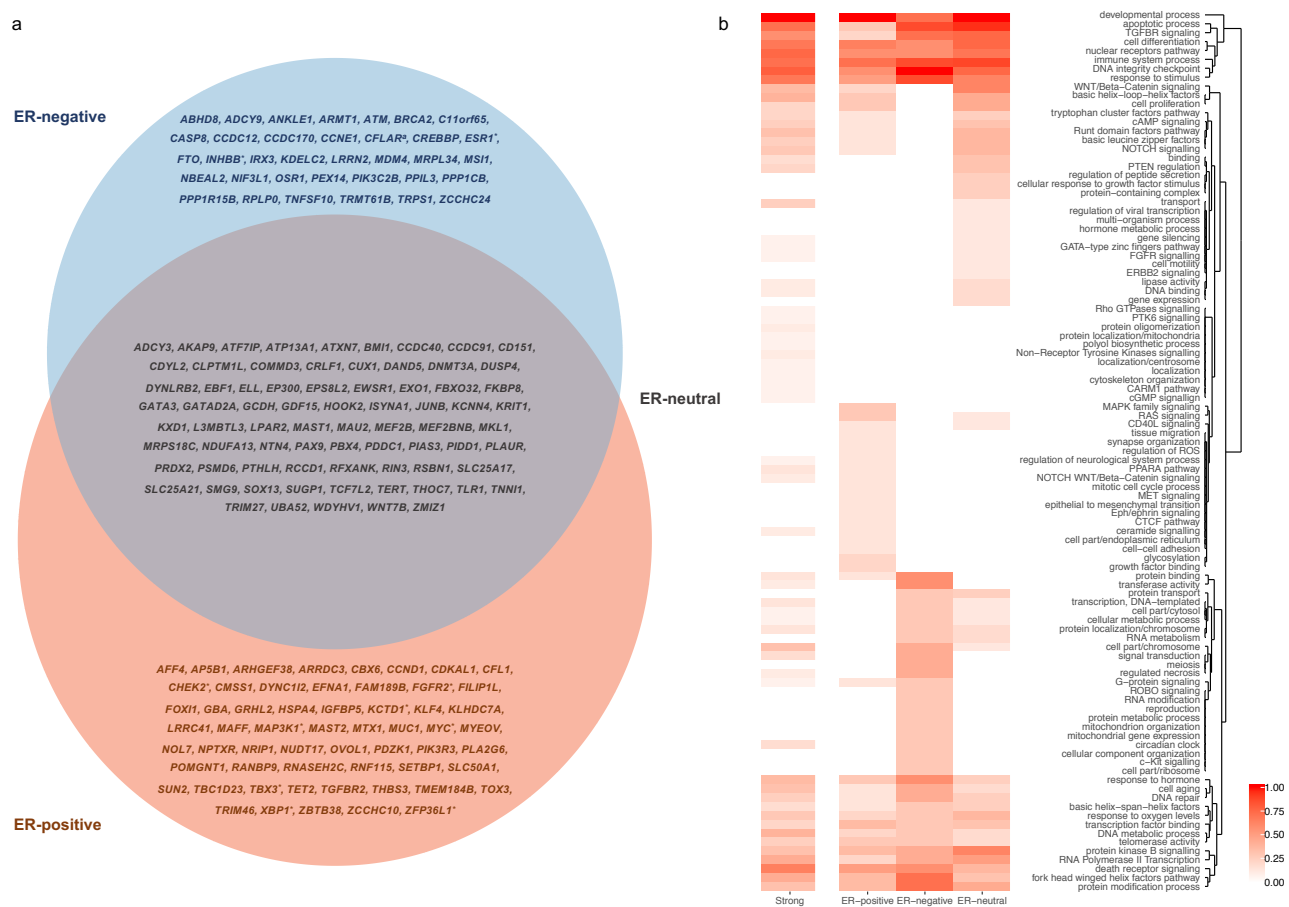


Figure 5. Predicted target genes by phenotype and significantly enriched pathways. (a) Venn diagram showing the associated phenotype (ER-positive, ER-negative, ER-neutral) for the Level 1 target genes, predicted by the CCVs and HPPVs. * ER-positive or ER-negative target genes also targeted by ER-neutral signals. (b) Heatmap showing clustering of pathway themes over-represented by INQUISIT Level 1 target genes. Color represents the relative number of genes per phenotype within enriched pathways, grouped by common themes. ER-positive, ER-negative, ER-neutral, and all phenotypes together (strong).

Novel pathways revealed by this study include TNF-related apoptosis-inducing ligand (TRAIL) signaling, the AP-2 transcription factors pathway, and regulation of I κ B kinase/NF- κ B signaling. Of note, the latter of these is specifically over-represented among ER-negative target genes. We also found significant

overrepresentation of additional carcinogenesis-linked pathways including cAMP, NOTCH, PI3K, RAS, WNT/Beta-catenin, and of receptor tyrosine kinases signaling, including FGFR, ERBB, or TGFBR⁴³⁻⁴⁷. Also of note, our target genes are significantly overrepresented in DNA damage checkpoint, DNA repair pathways, as well as programmed cell death pathways, such as apoptotic process, regulated necrosis, and death receptor signaling-related pathways.

DISCUSSION

We have performed multiple, complementary analyses on 150 breast cancer associated regions, originally found by GWAS, and identified 362 independent risk signals, 205 of these with high confidence (p-value < 10⁻⁶). We observed most regions contain multiple independent signals, the greatest number (nine) in the region surrounding *ESR1* and its co-regulated genes, and on 2q35, where *IGFBP5* appears to be a key target. We have used two complementary approaches to identify likely causal variants within each region: a Bayesian approach, PAINTOR, which integrated genetic associations, LD and informative genomic features, confirmed most associations found by the more traditional, multinomial regression approach, and also identified additional variants. Specifically, the Bayesian method highlighted 15 variants that are highly likely to be causal (HPP ≥ 80%). From these approaches we have identified a single variant, likely to be causal, at each of 34/205 signals (**Table 1**). Of these, only rs16991615 (*MCM8* p.E341K) and rs7153397 (*CCDC88C*, a cryptic splice-donor site) were predicted to affect protein-coding sequences. However, in other signals we also identified four coding changes previously recognized as deleterious, including the stop-gain rs11571833 (*BRCA2* p.K3326*, Meeks et al., 2016)⁴⁸ and two *CHEK2* coding variants; the frameshift rs555607708^{49,50}, and a missense variant, rs17879961^{51,52}. In addition, a splicing variant, rs10069690, in *TERT* results in the truncated

protein INS1b ¹⁹, decreased telomerase activity, telomere shortening, and increased DNA damage response ⁵³

Having identified potential causal variants within each signal, we aimed to uncover their functions at the DNA level and as well as trying to predict their target gene(s). Looking across all 150 regions, a notable feature is that many likely causal variants implicated in ER-positive cancer risk, lie in gene-regulatory regions marked as open and active in ER-positive breast cells, but not in other cell types. Moreover, a significant proportion of potential causal variants overlap the binding sites for transcription factor proteins (n=40 from ChIP-Seq) and co-regulators (n=64 with addition of computationally derived motifs). Furthermore, nine proteins also appear in the list of high-confidence target genes, hence the following genes and their products have been implicated by two different approaches: *CREBBP*, *EP300*, *ESR1*, *FOXI1*, *GATA3*, *MEF2B*, *MYC*, *NRIP1* and *TCF7L2*. Most of these proteins already have established roles in estrogen signaling. *CREBBP*, *EP300*, *ESR1*, *GATA3*, and *MYC* are also known cancer driver genes that are frequently somatically mutated in breast tumors.

In contrast to ER-positive signals, we identified fewer genomic features enriched in ER-negative signals. This may reflect the common molecular mechanisms underlying their development, but the power of this study was limited, despite including as many patients with ER-negative tumors as possible from the BCAC and CIMBA consortia. Less than 20% of genomic signals confer a greater risk of ER-negative cancer and there is little publicly available ChIP-Seq data on ER-negative breast cancer cell lines. The heterogeneity of ER-negative tumors may also have limited our power. Nevertheless, we have identified 35 target genes for ER-negative likely causal variants. Some of these already had functional

evidence supporting their role: including *CASP8*⁵⁴ and *MDM4*⁵⁵. Most targets, however, currently have no reported function in ER-negative breast cancer development.

Finally, we examined the gene-ontology pathways in which target genes most often lie. Of note, 12% (20/167) of all high-confidence target genes and 17% of ER-negative target predictions are in immune system pathways. Among the significantly enriched pathways were T cell activation, interleukin signaling, Toll-like receptor cascades, and I- κ B kinase/NF- κ B signaling, as well as processes leading to activation and perpetuation of the innate immune system. The link between immunity, inflammation and tumorigenesis has been extensively studied⁵⁶, although not primarily in the context of susceptibility. Four ER-negative high confidence target genes (*CASP8*, *CFLAR*, *ESR1*, *TNFSF10*) lie in the I- κ B kinase/NF- κ B signaling pathway. Interestingly, ER-negative cells have high levels of NF- κ B activity when compared to ER-positive⁵⁷. A recent expression–methylation analysis on breast cancer tumor tissue also identified clusters of genes correlated with DNA methylation levels, one enriched in ER signaling genes, and a second in immune pathway genes⁵⁸.

These analyses provide strong evidence for more than 200 independent breast cancer risk signals, identify the plausible cancer variants and define likely target genes for the majority of these. However, notwithstanding the enrichment of certain pathways and transcription factors, the biological basis underlying most of these signals remains poorly understood. Our analyses provide a rational basis for such future studies into the biology underlying breast cancer susceptibility.

METHODS

Study samples

Epidemiological data for European women were obtained from 75 breast cancer case-control studies participating in the Breast Cancer Association Consortium (BCAC) (cases: 40,285 iCOGS, 69,615 OncoArray; cases with ER status available: 29,561 iCOGS, 55,081 OncoArray); controls: 38,058 iCOGS, 50,879 OncoArray). Details of the participating studies, genotyping calling and quality control are given in ^{2,22,23}, respectively. Epidemiological data for *BRCA1* mutation carriers were obtained from 60 studies providing data to the Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2* (CIMBA) (affected 1,591 iCOGS, 7,772 OncoArray; unaffected 1,665 iCOGS, 7,780 OncoArray). This dataset has been described in detail previously ^{1,59,60}. All studies provided samples of European ancestry. Any non-European samples were excluded from analyses.

Variant selection, genotyping and imputation

A dense set of variants surrounding susceptibility variants known at the time of design was selected for genotyping on the iCOGS array. To select markers for comprehensive interrogation of these densely-genotyped regions, all known variants from the March 2010 release of the 1000 Genomes Project with MAF > 0.02 in Europeans were identified, and all variants that were correlated with the published GWAS variants at $r^2 > 0.1$ together with a set of variants designed to tag all remaining variants at $r^2 > 0.9$ were selected. Twenty-one regions were densely genotyped with iCOGS (http://ccge.medschl.cam.ac.uk/files/2014/03/iCOGS_detailed_lists_ALL1.pdf). In total 26,978 iCOGS genotyped variants across the 152 mapped regions passed QC criteria. Similarly, all known associated risk variants at the time of the design of the OncoArray were included in the genotyping array. Variants

for fine-mapping were selected defining a 1Mb interval surrounding a known hit. Overlapping regions were merged into a single interval including 500kb either side of each lead signal. From among designable variants, all variants correlated with the known hits at $r^2 > 0.6$, all variants from lists of potentially functional variants, defined through RegulomeDB, and a set of variants designed to tag all remaining variants at $r^2 > 0.9$ were selected. Seventy-three regions were densely genotyped with OncoArray. In total 58,339 OncoArray genotyped variants across the 152 mapped regions passed QC criteria.

We imputed genotypes for the remaining variants at the genomic regions defined in the OncoArray design using IMPUTE2⁶¹, and the October 2014 release of the 1000 Genomes Project as a reference. To improve the accuracy at low frequency variants we used the standard IMPUTE2 MCMC algorithm for follow-up imputation (more detailed description of the parameters used can be found in²¹) We genotyped or successfully imputed 639,118 variants all having imputation info score ≥ 0.3 and minor allele frequencies (MAF) ≥ 0.001 in both the iCOGS and OncoArray datasets. Imputation summaries, and coverage for each of the analyzed regions stratified by allele frequency can be found in **Supplementary Table 1B**.

BCAC Statistical analyses

Per-allele odds ratios (OR) and standard errors (SE) were estimated for each variant using logistic regression. We ran this analysis separately for iCOGS and OncoArray, and separately for overall, ER-positive and ER-negative breast cancer. The association between each variant and breast cancer risk was adjusted by study (iCOGS) or country (OncoArray), and eight (iCOGS) or ten (OncoArray) ancestry-

informative principal components. The statistical significance for each variant was derived using a Wald test.

Defining the significance threshold

To establish an appropriate significance threshold for independent signals, all variants evaluated in the meta-analysis were included in logistic forward selection regression analyses for overall breast cancer risk in iCOGS cohort, run independently for each of the regions. We evaluated five p-value thresholds for inclusion: $< 1 \times 10^{-4}$, $< 1 \times 10^{-5}$, $< 1 \times 10^{-6}$, $< 1 \times 10^{-7}$, and $< 1 \times 10^{-8}$. The most parsimonious iCOGS models were tested in OncoArray, and the false discovery rate (FDR) at 1% level for each one of the thresholds was estimated using the Benjamini-Hochberg procedure⁶². At a 1% FDR threshold, 72% of variants of variants significant at $p < 10^{-4}$ replicated on the OncoArray, whereas 94% of variants significant at $p < 10^{-6}$ replicated. Based on these analyses, two categories were defined: strong-evidence signals (conditional p-values $< 10^{-6}$ when the signal is included in the final model fit using the inclusion threshold $p < 10^{-4}$), and moderate-evidence signals (conditional p-values $< 10^{-4}$ and $\geq 10^{-6}$ in the final model).

Identification of independent signals

To identify independent signals, we ran multinomial stepwise regression analyses, separately in iCOGS and OncoArray, for all the variants displaying evidence of association ($N_{\text{variants}} = 202,749$). We selected two sets of well imputed variants (imputation info score ≥ 0.3 in both iCOGS and OncoArray): (a) common and low frequency variants ($MAF \geq 0.01$) with a threshold for inclusion of logistic regression p-value ≤ 0.05 in either the iCOGS or OncoArray datasets for at least one of the three phenotypes: overall, ER-positive and ER-negative breast cancer; and (b) rarer variants ($MAF \geq 0.001$ and < 0.01), with a threshold for inclusion of a logistic regression p-value ≤ 0.0001 . The same parameters used for adjustment in logistic regression were used in the multinomial regression analysis (R function

multinom). The multinomial regression estimates were combined using a fixed-effects meta-analysis weighted by the inverse variance⁶³. Variants with the lowest conditional p-value from the meta-analysis of both European cohorts at each step were included into the multinomial regression model. However, if the new variant to be included in the model caused collinearity problems due to be highly correlated with an already selected variant, or showed high heterogeneity ($p\text{-value} < 10^{-4}$) between iCOGS and OncoArray after being conditioned by the variant(s) in the model; we dropped the new variant and repeated this process.

The main signal at 105 of 152 evaluated regions demonstrated genome-wide significance, while 44 were marginally significant ($9.89 \times 10^{-5} \geq p\text{-value} > 5 \times 10^{-8}$). For two regions there were no variants significant at $p < 10^{-4}$ (chr14:104712261-105712261; rs10623258 multinomial regression $p\text{-value} = 2.32 \times 10^{-4}$; chr19:10923703-11923703, rs322144, multinomial regression $p\text{-value} = 3.90 \times 10^{-3}$). There are four main differences in the dataset used in the analysis and that used in the previous paper that account for these differences : (i) our previous paper² included data from 11 additional GWAS studies (14,910 cases and 17,588 controls) that have not been included in the present analysis in order to minimize differences in array coverage; (ii) the present analysis evaluated the risk of ER-positive and ER-negative disease concurrently, whereas in our previous paper the outcome was overall breast cancer risk. ER status was available for only 73% of the iCOGS and 79% of the OncoArray breast cancer cases (iii) for the set of samples genotyped with both arrays, ² included iCOGS genotypes, while this study includes OncoArray genotypes to maximize the number of samples genotyped with a larger coverage; and (iv) imputation parameters at fine mapping-regions were modified to improve the imputation accuracy of less frequent variants.

Selection of a credible set of variants candidates to be causal

Variants with p-values within two orders of magnitude of the top variant for each signal, after adjusting for the index variant of preceding signals, were considered as the credible set of candidates to drive the association at each independent signal (CCVs) ²⁴We defined the best model, among those including one CCVs for each signal, by iteratively conditioning on the selected CCVs in the other signals. For ten fine mapping regions (chr4:175328036-176346426, chr5:55531884-56587883, chr6:151418856-152937016, chr8:75730301-76917937, chr10:80341148-81387721, chr10:122593901-123849324, chr12:115336522-116336522, chr14:36632769-37635752, chr16:3606788-4606788, chr22:38068833-39859355) a model including the lowest conditioned p-value variants (index variant) at each signal could not be found. In that case we estimated the best model as the model with the largest chi-square, from all the possible combinations of credible variants. Variants in strong signals were conditioned by the additional strong confidence signals whereas variants for moderate confidence signals were conditioned by all the independent signals. We then redefined the credible set of candidate variants for each signal using the conditional p-values by the additional independent signals. Thus, variants with p-values within two orders of magnitude of the top variant for each signal, after adjusting for all the index variant of the additional signals at the locus, were considered as the final credible set of candidates.

Case -only analysis

Differences in the effect size between ER-positive and ER-negative disease for each index independent variant were assessed using a case-only analysis. We performed logistic regression with ER status as the

dependent variable, and the lead variant at each strong signal in the fine mapping region as the independent variables. We use FDR (5%) to adjust for multiple testing.

OncoArray-only stepwise analysis

To evaluate whether the lower coverage in iCOGS could affect the identification of independent signals, we ran stepwise multinomial regression using only the OncoArray dataset. We identified 249 independent signals. Ninety-two signals, in 67 fine mapping regions, achieved a genome-wide significance level (conditional p-value < 5×10^{-8}). Two hundred and five of these signals were also identified in the meta-analysis with iCOGS. Nine independent variants across ten regions were not evaluated in the combined analysis due to their low imputation info score in iCOGS. Out of these nine signals, two signals would be classified as main primary signals, rs114709821 at region chr1:145144984-146144984 (OncoArray imputation info score = 0.72), and rs540848673 at region chr1:149406413-150420734 (OncoArray imputation info score = 0.33). Given the low number of additional signals identified in the OncoArray dataset alone, all analyses were based on the combined iCOGS/OncoArray dataset.

CIMBA statistical analysis

CIMBA provided data from 60 retrospective cohort studies consisting of 9,445 unaffected and 9,363 affected female *BRCA1* mutation carriers of European ancestry. Unconditional (i.e. single variant) analyses were performed using a score test based on the retrospective likelihood of observing the genotype conditional on the disease phenotype^{64,65}. Conditional analyses, where more than one variant is analyzed simultaneously, cannot be performed in this score test framework. Therefore,

conditional analyses were performed by Cox regression, allowing for adjustment of the conditionally independent variants identified by the BCAC/DRIVE analyses. All models were stratified by country and birth cohort, and adjusted for relatedness (unconditional models used kinship adjusted standard errors based on the estimated kinship matrix; conditional models used cluster robust standard errors based on phenotypic family data).

Data from the iCOGS array and the OncoArray were analyzed separately and combined to give an overall *BRCA1* association by fixed-effects meta-analysis. Variants were excluded from further analyses if they exhibited evidence of heterogeneity (Heterogeneity p-value < 1×10^{-4}) between iCOGS and OncoArray, had MAF < 0.005, were poorly imputed (imputation info score < 0.3) or were imputed to iCOGS only (i.e. must have been imputed to OncoArray or iCOGS and OncoArray).

Meta-analysis of ER-negative cases in BCAC with *BRCA1* mutation carriers from CIMBA

BRCA1 mutation carrier association results were combined with the BCAC multinomial regression ER-negative association results in a fixed-effects meta-analysis. Variants considered for analysis must have passed all prior QC steps and have had $MAF \geq 0.005$. All meta-analyses were performed using the METAL software ⁶⁶. Instances where spurious associations might occur were investigated by assessing the LD between a possible spurious association and the conditionally independent variants. High LD between a variant and a conditionally independent variant within its region causes model instability through collinearity and the convergence of the model likelihood maximization may not be reliable. Where the association appeared to be driven by collinearity, the signals were excluded.

eQTL analysis

Total RNA was extracted from normal breast tissue in formalin-fixed paraffin embedded breast cancer tissue blocks from 264 Nurses' Health Study (NHS) participants ³². Transcript expression levels were measured using the Glue Grant Human Transcriptome Array version 3.0 at the Molecular Biology Core Facilities, Dana-Farber Cancer Institute. Gene expression was normalized and summarized into Log₂ values using RMA (Affymetrix Power Tools v1.18.012); quality control was performed using GlueQC and arrayQualityMetrics v3.24.014. Genome-wide data on variants were generated using the Illumina HumanHap 550 BeadChip as part of the Cancer Genetic Markers of Susceptibility initiative ⁶⁷. Imputation to the 1000KGP Phase 3 v5 ALL reference panel was performed using MACH to pre-phase measured genotypes and minimac to impute.

Expression analyses were performed using data from The Cancer Genome Atlas (TCGA) and Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) projects ^{34,38}. The TCGA eQTL analysis was based on 458 breast tumors that had matched gene expression, copy number and methylation profiles together with the corresponding germline genotypes available. All 458 individuals were of European ancestry as ascertained using the genotype data and the Local Ancestry in admixed Populations (LAMP) software package (LAMP estimate cut-off >95% European)⁶⁸. Germline genotypes were imputed into the 1000 Genomes Project reference panel (October 2014 release) using IMPUTE version 2 ^{69,70}. Gene expression had been measured on the Illumina HiSeq 2000 RNA-Seq platform (gene-level RSEM normalized counts ⁷¹), copy-number estimates were derived from the Affymetrix SNP 6.0 (somatic copy-number alteration minus germline copy-number variation called using the GISTIC2 algorithm ⁷²), and methylation beta values measured on the Illumina Infinium HumanMethylation450.

Expression QTL analysis focused on all variants within each of the 152 genomic intervals that had been subjected to fine-mapping for their association with breast cancer susceptibility. Each of these variants was evaluated for its association with the expression of every gene within 2 Mb that had been profiled for each of the three data types. The effects of tumor copy number and methylation on gene expression were first regressed out using a method described previously ⁷³. eQTL analysis was performed by linear regression, with residual gene expression as outcome, germline SNP genotype dosage as the covariate of interest and ESR1 expression and age as additional covariates, using the R package Matrix eQTL ⁷⁴.

The METABRIC eQTL analysis was based on 138 normal breast tissue samples resected from breast cancer patients of European ancestry. Germline genotyping for the METABRIC study was also done on the Affymetrix SNP 6.0 array, and gene expression in the METABRIC study was measured using the Illumina HT12 microarray platform (probe-level estimates). No adjustment was implemented for somatic copy number and methylation status since we were evaluating eQTLs in normal breast tissue. All other steps were identical to the TCGA eQTL analysis described above.

Genomic feature enrichment

We explored the overlap of candidate and excluded variants with 90 transcription factors, 10 histone marks, and DNase hypersensitivity sites in 15 breast cell lines, and eight normal human breast tissues. We analysed data from the Encyclopedia of DNA Elements (ENCODE) Project ^{75,76}, Roadmap Epigenomics Projects ⁷⁷, the International Human Epigenome Consortium ^{78, 27, 79}, The Cancer Genome Atlas (TCGA) ³³, the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) ³⁴, ReMap database (We included 241 TF annotations from ReMap (of 2825 total) which

showed at least 2% overlap for any of the phenotype SNP sets)⁸⁰, and other data obtained through the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO). Promoters were defined following the procedure defined in Pellacani et al.⁷⁹, that is +/- 2Kb from a gene transcription start site, using an updated version of the RefSeq genes (refGene, version updated 2017-04-11)⁸¹. Transcribed regions were defined using the same version of refSeq genes. lncRNA annotation was obtained from GENCODE (v19)⁸²

To include eQTL results in the enrichment analysis we (i) identified all the genes for which summary statistics were available, for each study; (ii) defined the most significant eQTL variant for each gene (index eQTL variant, p-value threshold $\leq 5 \times 10^{-4}$); (iii) classified variants with p-values within two orders of magnitude of the index eVariant as the credible set of eQTL variants candidate to drive the expression of the gene. Those variants part of at least one eQTL credible set were defined as eVariants. We evaluated the overlap between eQTL credible sets and CCVs (risk variants credible set). We evaluated the enrichment of CCVs for genomic feature using logistic regression, with CCV (vs non-CCV variants) being the outcome. To adjust for the correlation among variants in the same fine mapping region, we used robust variance estimation for clustered observations (R function *multiwaycov*). The associated variants at FDR 5% were included into a stepwise forward logistic regression procedure to select the most parsimonious model. A likelihood ratio test was used to compare multinomial logistic regression models with and without equality effect constraints to evaluate whether there was heterogeneity among the effect sizes for ER-positive, ER-negative or signals equally associated with both phenotypes (ER-neutral).

To validate the disease specificity of the regulatory regions identified through this analysis we follow the same approach for the autoimmune related CCVs from ²⁹ (N = 4,192). Variants excluded as candidate causal variants, and within 500 kb upstream and downstream of the index variant for each signal were classified as excluded variants (N = 1,686,484). We then tested the enrichment for both the breast cancer and autoimmune CCVs with breast and T and B cell enhancers. We also evaluated the overlap of our CCVs with ENCODE enhancer-like and promoter-like regions for 111 tissues, primary cells, immortalized cell line, and in vitro differentiated cells. Of these, 73 had available data for both enhancer- and promoter-like regions.

Transcription binding site motif analysis

We conducted a search to find motif occurrences for the transcription factors significantly enriched in the genomic featured. For this we used two publicly available databases, Factorbook ⁸³ and JASPAR 2016 ⁸⁴. For the search using Factorbook we included the motifs for the transcription factors discovered in the cell lines where a significant enrichment was found in our genomic features analysis. We also searched for all the available motifs for *Homo sapiens* at the JASPAR database (*JASPAR CORE 2016, TFBSTools* ⁸⁵) Using as reference the USCS sequence (*BSgenome.Hsapiens.USCS.hg19*) we created fasta sequences with the reference and alternative alleles for all the variants included in our analysis plus 20 bp flanking each variant. We used FIMO (version 4.11.2, Grant et al., 2011) ⁸⁶ to scan all the fasta sequences searching for the JASPAR and Factorbook motifs to identify any overlap of any of the alleles for each of the variants (setting the p-value threshold to 10^{-3}). We subsequently determined whether our CCVs were more frequency overlapping a particular TF binding motif when compared with the excluded variants. We ran these analyses for all the strong signals, but also strong signals stratified by

ER status. Also, we subset this analysis to the variants located at regulatory regions in an ER-positive cell line (MCF-7 marked by H3K4me1, ENCODE id: ENCFF674BKS) and evaluated whether the ER-positive CCVs overlap any of the motifs more frequently than the excluded variants. We also evaluated the change in total binding affinity caused by the ER-positive CCCR alternative allele for all but one (2:217955891:T:<CN0>:0) of the ER-positive CCVs (*MatrixRider*⁸⁷).

Subsequently, we evaluated whether the MCF-7 regions demarked by H3K4me1 (ENCODE id: ENCFF674BKS), and overlapped by ER-positive CCVs, were enriched in known TFBS motifs. We first subset the ENCODE bed file ENCFF674BKS to identify MCF-7 H3K4me1 peaks overlapped by the ER-positive CCVs (N = 107), as well as peaks only overlapped by excluded variants (N = 11,099), using BEDTools⁸⁸. We created fasta format sequences using genomic coordinate data from the intersected bed files. In order to create a control sequence set, we used the script included with the MEME Suite (*fasta-shuffle-letters*) to create 10 shuffled copies of each sequence overlapped by ER-positive CCVs (N = 1,070). We then used AME⁸⁹ to interrogate whether the 107 MCF-7 H3K4me1 genomic regions overlapped by ER-positive CCVs were enriched in known TFBS consensus motifs when compared to the shuffled control sequences, or to the MCF-7 H3K4me1 genomic regions overlapped only by excluded variants. We used the command line version of AME (version 4.12.0) selecting as scoring method the total number of positions in the sequence whose motif score p-value is less than 10^{-3} , and using a one-tailed Fisher's Exact test as the association test.

PAINTOR analysis

To further refine the set of CCVs, we performed empirical Bayes fine-mapping using PAINTOR to integrate marginal genetic association summary statistics, linkage disequilibrium patterns, and biological features^{31,90}. PAINTOR places higher prior probability for causality on variants that fall in particular genomic features and learns the priors for different genomic features from the aggregate association results across all of the regions being mapped. PAINTOR does not assume a fixed number of causal variants in each region, although it implicitly penalizes non-parsimonious causal models. We applied PAINTOR separately to association results for overall breast cancer (in 85 regions determined to have at least one ER-neutral association or ER-positive and ER-negative association), ER-positive breast cancer (in 48 regions determined to have at least one ER-positive-specific association), and ER-negative breast cancer (in 22 regions determined to have at least one ER-negative-specific association). To avoid artifacts due to mis-matches between the LD in study samples and the LD matrix supplied to PAINTOR, we used association logistic regression summary statistics from OncoArray data only and estimated the LD structure in the OncoArray sample. For each endpoint we fit four models with increasing numbers of genomic features selected from the stepwise enrichment analyses described above: Model 0 (with no genomic features—assumes each variant is equally likely to be causal a priori), Model 1 (with those genomic features selected with stopping rule $p < 0.001$); Model 2 (with those genomic features selected with stopping rule $p < 0.01$); and Model 3 (with those genomic features selected with stopping rule $p < 0.05$).

We used the Bayesian Information Criterion (BIC) to choose the best-fitting model for each outcome. As PAINTOR estimates the marginal log likelihood of the observed Z scores using Gibbs sampling, we used a shrunk mean BIC across multiple Gibbs chains to account for the stochasticity in the log-

likelihood estimates. We ran PAINTOR four times to generate four independent Gibbs chains estimated the BIC difference between model i and model j as $\Delta_{ij} = \left(\frac{100}{V+100}\right)(BIC_i - BIC_j)$. This assumes a $N(0,100)$ prior on the difference, or roughly a 16% chance that model i would be decisively better than model j (i.e. $|BIC_i - BIC_j| > 10$). We then proceeded to choose the best-fitting model in a stepwise fashion: starting with a model with no annotations, we selected a model with more annotations in favor a model with fewer if the larger model was a considerably better fit—i.e. $\Delta_{ij} > 2$. Model 1 was the best fit according to this process for overall and ER-positive breast cancer; Model 0 was the best fit for ER-negative breast cancer.

Differences between the PAINTOR and CCV outputs may be due to several factors. By considering functional enrichment and joint LD among all SNPs, PAINTOR may refine the set of likely causal variants; rather than imposing a hard threshold, PAINTOR allows for a gradient of evidence supporting causality; and the two sets of calculations are based on different summary statistics, CCV analyses used both iCOGS and OncoArray genotypes, while PAINTOR used only OncoArray data (**Figure 1**, Methods).

Variant annotation

Variants genome coordinates were converted to assembly GRCh38 with liftOver and uploaded to Variant Effect Predictor ⁹¹ to determine their effect on genes, transcripts, and protein sequence. The commercial software Alamut[®] Batch v1.6 batch was also used to annotate coding and splicing variants. PolyPhen-2 ⁹², SIFT ⁹³, MAPP ⁹⁴ were used to predict the consequence of missense coding variants. MaxEntScan ⁹⁵, Splice-Site Finder, and Human Splicing Finder ⁹⁶ were used to predict splicing effects.

INQUISIT analysis

Logic underlying INQUISIT predictions

Briefly, genes were considered to potential targets of risk variants when variants affect: (1) distal regulation, (2) proximal genomic information, including chromatin interactions from capture Hi-C experiments performed in a panel of six breast cell lines ⁹⁷, chromatin interaction analysis by paired-end tag sequencing (ChIA-PET; ⁹⁸) and genome-wide chromosome conformation capture from HMECs (Hi-C, (Rao et al., 2014)). We used computational enhancer–promoter correlations (PreSTIGE ⁹⁹, IM-PET (He et al., 2014), FANTOM5 ¹⁰⁰ and super-enhancers ²⁸), results for breast tissue-specific expression variants (eVariants) from multiple independent studies (TCGA, METABRIC, NHS, Methods), allele-specific imbalance in gene expression ¹⁰¹, 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 as described above, gene expression RNA-seq from several breast cancer lines and normal samples and topologically associated domain (TAD) boundaries from T47D cells (ENCODE, ¹⁰², Methods and Key Resources Table). To assess the impact of intragenic variants, we evaluated their potential to alter splicing using Alamut® Batch to identify new and cryptic donors and acceptors, and several tools to predict effects of coding sequence changes (Methods). The output from each tool was converted to a binary measure to indicate deleterious or tolerated predictions.

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 points based on physical

links (eg ChI-C), computational prediction methods, allele-specific expression, or eVariant associations. All CCV and HPPVs were considered as potentially involved in distal regulation. Intersection of a putative distal enhancer with genomic features found to be significantly enriched (see '**Genomic features enrichment**' for details) were further upweighted. CCVs and HPPVs 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 eVariant association or allele-specific expression, 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. For each category, scores ranged from 0-7 (distal); 0-3 (promoter) or 0-2 (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. Driver and transcription factor gene enrichment analysis was carried out using INQUISIT scores prior to adding a point for driver gene status. Modifications to the pipeline since original publication ² include:

- TAD boundary definitions from ENCODE T47D Hi-C analysis. Previously, we used regions from Rao, Cell 2013;
- eQTL: Addition of NHS normal and tumor samples

- allele-specific imbalance using TCGA and GTEx RNA-seq data ¹⁰¹
- Capture Hi-C data from six breast cell lines (Beesley et al.)
- Additional biofeatures derived from global enrichment in this study.

Multi-signal targets

To test if more genes were targeted by multiple signals than expected by chance, we modelled the number of signals per gene by negative binomial regression (R function *glm.nb*, package MASS) and Poisson regression (R function *glm*, package stats) with ChIA-PET interactions as a covariate and adjusted by fine mapping region. Likelihood ratio tests were used to compare goodness of fit. Rootograms were created using the R function *rootogram* (package vcd).

Pathway analysis

The pathway gene set database, dated 1 September 2018 was used ¹⁰³ (http://download.baderlab.org/EM_Genesets/current_release/Human/symbol/). This database contains pathways from Reactome ¹⁰⁴, NCI Pathway Interaction Database ¹⁰⁵, GO (Gene Ontology) ¹⁰⁶, HumanCyc ¹⁰⁷, MSigdb ¹⁰⁸, NetPath ¹⁰⁹, and Panther ¹¹⁰. All duplicated pathways, defined in two or more databases, were included. To provide more biologically meaningful results, only pathways that contained ≤ 200 genes were used.

We interrogated the pathway annotation sets with the list of high-confidence (Level 1) INQUISIT gene list. The significance of over-representation of the INQUISIT genes within each pathway was assessed with a hypergeometric test, ¹¹¹, using the R function *phyper* as follows:

$$P(x|n, m, N) = 1 - \sum_{i=0}^{x-1} \frac{\binom{m}{i} \binom{N-m}{n-i}}{\binom{N}{n}}$$

where x is the number of Level 1 genes that overlap with any of the genes in the pathway, n is the number of genes in the pathway, m is the number of Level1 genes that overlap with any of the genes in the pathway data set ($m_{\text{strong GO}} = 135$, $m_{\text{ER-positive GO}} = 48$, $m_{\text{ER-negative GO}} = 26$, $m_{\text{ER-neutral GO}} = 73$; $m_{\text{strong Pathways}} = 114$, $m_{\text{ER-positive Pathways}} = 36$, $m_{\text{ER-negative Pathways}} = 21$, $m_{\text{ER-neutral Pathways}} = 67$), and N is the number of genes in the pathway data set ($N_{\text{Genes GO}} = 14,252$, $N_{\text{Genes Pathways}} = 10,915$). We only included pathways that overlapped with at least two Level 1 genes. We used the Benjamini-Hochberg false discovery rate (FDR) ⁶² at 5% level.

ACKNOWLEDGMENTS

We thank all the individuals who took part in these studies and all the researchers, clinicians, technicians and administrative staff who have enabled this work to be carried out. This work was supported by the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 656144. Genotyping of the OncoArray was principally funded from three sources: the PERSPECTIVE project, funded by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, the 'Ministère de l'Économie, de la Science et de l'Innovation du Québec' through Genome Québec, and the Quebec Breast Cancer Foundation; the NCI Genetic Associations and Mechanisms in Oncology (GAME-ON) initiative and Discovery, Biology and Risk of Inherited Variants in Breast Cancer (DRIVE) project (NIH Grants U19 CA148065 and X01HG007492); and Cancer Research UK (C1287/A10118 and C1287/A16563). BCAC is funded by

Cancer Research UK (C1287/A16563), by the European Community's Seventh Framework Programme under grant agreement 223175 (HEALTH-F2-2009-223175) (COGS) and by the European Union's Horizon 2020 Research and Innovation Programme under grant agreements 633784 (B-CAST) and 634935 (BRIDGES). Genotyping of the iCOGS array was funded by the European Union (HEALTH-F2-2009-223175), Cancer Research UK (C1287/A10710), the Canadian Institutes of Health Research for the 'CIHR Team in Familial Risks of Breast Cancer' program, and the Ministry of Economic Development, Innovation and Export Trade of Quebec, grant PSR-SIIRI-701. Combining of the GWAS data was supported in part by The National Institute of Health (NIH) Cancer Post-Cancer GWAS initiative grant U19 CA 148065 (DRIVE, part of the GAME-ON initiative). For a full description of funding and acknowledgments, see Supplementary Note.

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A.G.N., M.H.G., M.Gr., J.Gr., A.G., P.G., E.H., C.A.H., N.H., P.Ha., U.H., P.A.H., J.M.H., M.H., W.H., C.S.H., B.A.M., J.H., P.Hi., F.B.L., A.H., M.J.H., J.L.H., A.Ho., G.H., P.J.H., E.N.I., C.I., M.I., A.Jag., M.J., A.Jak., P.J., R.J., R.C.J., E.M.J., N.J., M.E.J., A.Juk., A.Jun., R.Ka., D.K., B.Pes., R.Ke., M.J.K., E.K., J.I.K., J.K., C.M.K., Y.K., I.K., V.K., S.Ko., K.K.S., T.K., A.K., K.K., Y.L., D.L., E.L., G.L., J.Le., F.L., A.Li., W.L., J.Lo., A.Lo., J.T.L., J.Lu., R.J.M., T.M., E.M., A.Ma., M.Ma., S.Man., S.Mag., M.E.M., K.Ma., D.M., R.M., L.M., C.M., N.Me., A.Me., P.M., A.Mi., N.Mi., M.Mo., F.M., A.M.M., V.M.M., T.A., S.A.N., R.N., K.L.N., N.Z.N., H.N., P.N., F.C.N., L.N.Z., A.N., K.O., E.O., O.I.O., H.O., N.O., A.O., V.S.P., J.Pa., S.K.P., T.W.P.S., M.T.P., J.Pau., I.S.P., B.Pei., B.Y.K., P.P., J.Pe., D.P.K., K.Pr., R.P., N.P., D.P., M.A.P., K.Py., P.R., S.J.R., J.R., R.R.M., G.R., H.A.R., M.R., A.R., C.M.R., E.S., E.S.H., D.P.S., M.Sa., C.Sa., E.J.S., M.T.S., D.F.S., R.K.S., A.S., M.J.S., B.S., P.Sc., C.Sc., R.J.S., L.S., C.M.D., M.Sh., P.Sh., C.Y.S., X.S., C.F.S., T.P.S., S.S., M.C.S., J.J.S., A.B.S., J.St., D.S.L., C.Su., A.J.S., R.M.T., Y.Y.T., W.J.T., J.A.T., M.R.T., M.Te., S.H., M.B.T., A.T., M.Th., D.L.T., M.G.T., M.Ti., A.E.T., R.A.E., I.T., D.T., G.T.M., M.A.T., N.T., M.Tz., H.U.U., C.M.V., C.J.A., L.E.K., E.J.R., A.Ve., A.Vi., J.V., M.J.V., Q.W., B.W., C.R.W., J.N.W., C.W., H.W., R.W., A.W., A.H.W., D.Y., Y.Z., W.Z. Data management and curation: K.Mi., J.D., M.K.B., Q.W., R.Ke., J.C.C. and M.K.S. Writing original draft: L.Fa., H.As., J.Be., G.C.T., D.F.E., P.K., A.M.D. Writing review and editing: D.R.B., J.Al., P.So., A.Le., V.N.K., J.D.E., S.L.E., A.C.A., J.Si. Visualization: L.Fa., H.As., J.Be., C.Tu. Supervision: A.C.A., G.C.T., J.Si., D.F.E., P.K., A.M.D. Funding acquisition: L.Fa., P.D.P.P., J.C.C., M.G.C., M.K.S., R.L.M., V.N.K., J.D.E., S.L.E., A.C.A., G.C.T., J.Si., D.F.E., P.K., A.M.D. All authors read and approved the final version of the manuscript.

COMPETING INTERESTS STATEMENT

The authors declare no competing interests.

MATERIALS & CORRESPONDENCE

Further information and requests for resources should be directed to and will be fulfilled by Manjeet Bolla (bcac@medschl.cam.ac.uk)

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Table 1. Signals with single CCVs and variants with PP > 80%

Fine-mapping region ^a	Variant ^b	Ref/Alt ^c	EAF ^d	PP ^e	Model ^f	Signal ^g	N CCV ^h	ER-negative		ER-positive		P-value ⁱ	FP ^j	Predicted target gene(s) ^k	Confidence ^l
								OR ⁱ	(95%CI)	OR ⁱ	(95%CI)				
chr1:120723447-121780613	rs11249433	A/G	0.42	0.57	ERALL	Signal 1	1	1.02	(0.99-1.04)	1.13	(1.11-1.15)	8.11x10 ⁻⁶⁰	na	na	
chr1:200937832-201937832	rs35383942	C/T	0.06	0.96	ERALL	Signal 1	2	1.10	(1.05-1.16)	1.09	(1.06-1.13)	1.14x10 ⁻⁷	D	<i>TNNI1</i>	Level 1
chr2:201681247-202681247	rs3769821	C/T	0.66	0.40	ERALL	Signal 1	1	0.94	(0.92-0.97)	0.95	(0.93-0.96)	1.46x10 ⁻¹²	D	<i>ALS2CR11</i> , <i>ALS2CR12</i> , <i>CASP8^m</i> , <i>MPP4</i> , <i>NIF3L1</i> , <i>STRADB</i> , <i>TMEM237</i>	Level 2
chr2:217405832-218796508	rs4442975	G/T	0.48	0.84	ERALL	Signal 1	1	0.94	(0.92-0.97)	0.86	(0.85-0.87)	2.50x10 ⁻⁹⁰	D	<i>IGFBP5^m</i>	Level 1
chr4:105569013-106856761	esv3601665	-/Alu	0.07	0.95	ERPOS			1.01	(0.95-1.08)	1.10	(1.06-1.14)	3.27x10 ⁻⁶	D	<i>ARHGEF38</i> , <i>AC004066.3</i>	Level 1
chr5:779790-1797488	rs10069690	C/T	0.27	0.58	ERNEG	Signal 1	1	1.18	(1.15-1.21)	1.03	(1.01-1.05)	1.20x10 ⁻³⁴	D	<i>CLPTM1L</i> , <i>TERT^m</i>	Level 1
chr5:44013304-45206498	rs10941679	A/G	0.26	0.00	ERPOS	Signal 1	1	1.04	(1.02-1.07)	1.17	(1.15-1.19)	1.50x10 ⁻⁷⁷	D	<i>MRPS30</i>	Level 2
	rs5867671	A/-	0.77	0.01	ERPOS	Signal 2	1	0.91	(0.89-0.94)	0.99	(0.97-1.01)	2.25x10 ⁻⁹	na	na	
chr5:44013304-45206498	rs190443933	T/C	0.01	0.00	ERALL	Signal 4	1	1.30	(1.14-1.48)	1.26	(1.16-1.37)	2.32x10 ⁻⁸	na	na	
chr5:55531884-56587883	rs984113	G/C	0.61	0.81	ERPOS	Signal 2	1	0.96	(0.93-0.98)	0.96	(0.94-0.97)	3.51x10 ⁻⁸	D	<i>MAP3K1^m</i>	Level 1
	rs889310	C/T	0.56	0.84	ERPOS	(Signal 6)	15	1.03	(1.00-1.05)	1.05	(1.03-1.06)	1.75x10 ⁻⁷	D	<i>MAP3K1^m</i>	Level 1
chr6:15899557-16899557	rs3819405	C/T	0.32	0.96	ERALL	Signal 1	1	0.97	(0.95-1.00)	0.95	(0.94-0.97)	1.14x10 ⁻⁷	D	<i>ATXN1</i> , <i>RP1-151F17.1</i> , <i>RP1-151F17.2</i>	Level 2
chr6:151418856-152937016	rs12173562	C/T	0.08	0.10	ERNEG	Signal 1	1	1.30	(1.25-1.36)	1.14	(1.11-1.18)	3.98x10 ⁻⁴⁰	D	<i>ESR1^m</i>	Level 1
	rs34133739	-/C	0.53	0.25	ERALL	Signal 2	1	1.11	(1.09-1.14)	1.05	(1.04-1.07)	2.36x10 ⁻²²	D	<i>ESR1^m</i> , <i>SYNE1</i>	Level 2
	rs851984	G/A	0.40	0.73	ERALL	Signal 3	1	1.07	(1.04-1.09)	1.05	(1.04-1.07)	3.69x10 ⁻¹³	D	<i>ESR1^m</i>	Level 1
chr7:130167121-131167121	rs68056147	G/A	0.30	0.84	ERALL			1.04	(1.01-1.07)	1.05	(1.03-1.06)	3.07x10 ⁻⁷	D	<i>MKLN1</i>	Level 2
chr8:127424659-130041931	rs35961416	-/A	0.41	0.68	ERALL	Signal 3	1	0.97	(0.94-0.99)	0.95	(0.93-0.96)	9.97x10 ⁻¹¹	D	<i>CASC11</i> , <i>MYC^m</i>	Level 2
chr9:21247803-22624477	rs539723051	AAAA/-	0.33	0.43	ERALL	Signal 1	1	1.08	(1.05-1.11)	1.06	(1.04-1.08)	1.81x10 ⁻¹⁵	na	na	

chr9:109803808-111395353	rs10816625	A/G	0.07	0.95	ERPOS	Signal 3	1	1.06	(1.01-1.11)	1.13	(1.10-1.16)	3.62x10 ⁻¹⁵	D	<i>KLF4^m</i>	Level 2
	rs13294895	C/T	0.18	0.93	ERPOS	Signal 4	1	1.01	(0.98-1.05)	1.09	(1.07-1.11)	4.00x10 ⁻¹⁷	D	<i>KLF4^m</i>	Level 1
chr9:109803808-111395353	rs60037937	AA/-	0.22	0.68	ERPOS	Signal 2	1	1.02	(0.99-1.06)	1.11	(1.09-1.13)	3.17x10 ⁻²⁶	D	<i>KLF4^m, RAD23B</i>	Level 2
chr10:63758684-65063702	rs10995201	A/G	0.15	0.31	ERALL	Signal 1	1	0.91	(0.88-0.94)	0.87	(0.85-0.89)	1.40x10 ⁻³⁷	na	na	
chr10:122593901-123849324	rs45631563	A/T	0.04	0.93	ERPOS	Signal 3	1	0.97	(0.92-1.03)	0.76	(0.73-0.79)	4.84x10 ⁻⁴⁴	C	<i>FGFR2^m</i>	Level 1
chr10:122593901-123849324	rs35054928	C/-	0.56	0.60	ERALL	Signal 1	1	0.96	(0.94-0.98)	0.74	(0.73-0.76)	6.55x10 ⁻³⁴²	D	<i>FGFR2^m</i>	Level 1
	rs45631563	A/T	0.04	0.93	ERPOS	Signal 3	1	0.97	(0.92-1.03)	0.76	(0.73-0.79)	4.84x10 ⁻⁴⁴	C	<i>FGFR2^m</i>	Level 1
	rs7899765	T/C	0.06	0.02	ERALL	Signal 5	1	1.01	(0.97-1.06)	0.87	(0.84-0.90)	2.21x10 ⁻¹⁸	D	<i>FGFR2^m</i>	Level 1
chr11:68831418-69879161	rs78540526	C/T	0.09	0.91	ERPOS	Signal 1	1	1.01	(0.97-1.06)	1.40	(1.36-1.44)	2.77x10 ⁻¹⁴⁵	D	<i>CCND1^m, MYEOV</i>	Level 1
chr12:27639846-29034415	rs7297051	C/T	0.23	0.23	ERALL	Signal 1	1	0.87	(0.85-0.90)	0.89	(0.88-0.91)	3.12x10 ⁻⁴³	D	<i>CCDC91^m, PTHLH^m, RP11-967K21.1</i>	Level 2
chr12:115336522-116336522	rs35422	G/A	0.57	0.58	ERPOS	Signal 2	1	0.98	(0.96-1.01)	1.05	(1.03-1.07)	4.85x10 ⁻¹⁰	D	<i>TBX3</i>	Level 1
chr14:91341069-92368623	rs7153397	C/T	0.70	0.81	ERPOS	Signal 1	3	1.01	(0.99-1.04)	1.06	(1.04-1.08)	3.25x10 ⁻¹¹	D,C	<i>CCDC88C, CTD-2547L24.4, GPR68, RP11-73M18.7, RP11-895M11.3</i>	Level 2
chr16:52038825-53038825	rs4784227	C/T	0.27	0.95	ERPOS	Signal 1	1	1.15	(1.12-1.18)	1.26	(1.24-1.28)	4.63x10 ⁻¹⁶⁰	D	<i>TOX3^m</i>	Level 1
chr18:23832476-25075396	rs180952292	T/C	0.01	0.01	ERNEG	Signal 4	1	1.24	(1.12-1.37)	0.98	(0.92-1.05)	2.07x10 ⁻⁵	na	na	
chr18:41899590-42899590	rs9952980	T/C	0.34	0.95	ERALL	Signal 2	3	0.97	(0.94-0.99)	0.95	(0.93-0.96)	7.43x10 ⁻¹²	D	<i>SETBP1</i>	Level 2
chr20:5448227-6448227	rs16991615	G/A	0.07	0.97	ERALL	Signal 1	1	1.09	(1.04-1.15)	1.07	(1.04-1.11)	7.89x10 ⁻⁷	D, C	<i>GPCPD1, MCM8</i>	Level 2
chr22:45783297-46783297	rs184070480	C/T	0.01	0.00	ERALL	Signal 2	1	1.40	(1.20-1.64)	1.01	(0.91-1.12)	5.02x10 ⁻⁵	D	<i>ATXN10, WNT7B</i>	Level 2

^a GRCh37/hg19, bp

^b Current reference ID

^c Reference (Ref) versus Alternative (Alt) Allele

^d Effect allele (Alt allele) frequency in OncoArray

^e PP: Posterior probability. Largest posterior probability in all evaluated models

^f Model where the variant reaches the largest posterior probability

^g Signal where the variant is included. Between brackets moderate confidence signals.

^h Number of CCVs in the signal

ⁱ Multinomial regression summary statistics. Single variant analysis

^j D: Distal regulation, P: proximal regulation, C: coding; na: prediction non available

^k Predicted target genes with the largest confidence level for each variant. Between brackets, largest confidence level. na: prediction non available

^l INQUISIT level of confidence

^m Target genes with functional follow up

Table 2. Regions in which target genes are predicted with high confidence

Fine-mapping region ^a	Signal / PP >30% ^b	N Variants ^c	Distal ^d	Promoter ^e	Coding ^f
chr1:10043820-11066215	Signal 1	19	<i>PEX14</i>		
chr1:18307339-19307339	Signal 1	12		<i>KLHDC7A</i>	
	PP > 30%	1		<i>KLHDC7A</i>	
chr1:46100917-47100917	Signal 1	11	<i>LRRC41, PIK3R3</i>		
	PP > 30%	2	<i>MAST2, POMGNT1</i>		
chr1:113948389-114948389	Signal 1	12	<i>RSBN1</i>		
chr1:145144984-146144984	Signal 1	35	<i>NUDT17, PDZK1, RNF115</i>		
	Signal 2	5	<i>PIAS3</i>		
chr1:154648781-155648781	Signal 1	16	<i>EFNA1, FAM189B, GBA, MTX1, MUC1, RP11-263K19.4, SLC50A1, THBS3, TRIM46</i>		
chr1:200937832-201937832	Signal 1	2	<i>TNNI1</i>		
	PP > 30%	2	<i>TNNI1</i>		
chr1:203301249-204301249	Signal 1	56	<i>SOX13</i>		
chr1:204018842-205018842	Signal 1	6	<i>LRRN2, MDM4, PIK3C2B, PPP1R15B</i>	<i>MDM4</i>	
chr1:241523898-242534263	Signal 1	2			<i>EXO1</i>
	PP > 30%	2			<i>EXO1</i>
chr2:18815791-19820803	Signal 1	17	<i>OSR1</i>		
chr2:24687599-25687599	Signal 1	92	<i>ADCY3, DNMT3A</i>		<i>DNMT3A</i>
chr2:28670676-29670676	Signal 1	81	<i>PPP1CB, TRMT61B</i>		
chr2:120745122-121746568	Signal 3	3	<i>INHBB</i>		
	Signal 4	6	<i>INHBB</i>		
	PP > 30%	3	<i>INHBB</i>		
chr2:171876221-173472971	Signal 2	35	<i>DYNC1I2</i>		
	PP > 30%	2	<i>DYNC1I2</i>		
chr2:201681247-202681247	Signal 2	8	<i>CFLAR</i>		
	CIMBA	154	<i>CASP8, CFLAR, NIF3L1, PPIL3</i>	<i>CASP8</i>	
chr2:217405832-218796508	PP > 30%	6	<i>IGFBP5</i>		
chr3:30175880-31175880	Signal 1	23			<i>TGFBR2</i>
chr3:46366866-47381488	CIMBA	16	<i>CCDC12, NBEAL2</i>		
chr3:63441697-64467900	Signal 1	94	<i>ATXN7, PSMD6, PSMD6-AS2, THOC7</i>		<i>ATXN7</i>
chr3:99223580-100223580	Signal 1	92	<i>CMSS1, FILIP1L, TBC1D23</i>		
chr3:140612859-141612859	Signal 1	24	<i>ZBTB38</i>		
chr3:171785237-172785237	CIMBA	36	<i>TNFSF10</i>		
chr4:38312876-39312876	Signal 1	24			<i>TLR1</i>
chr4:83870124-84870124	Signal 1	84	<i>MRPS18C</i>	<i>MRPS18C</i>	
chr4:105569013-106856761	Signal 1	21	<i>TET2</i>		<i>TET2</i>
	PP > 30%	1	<i>AC004066.3, ARHGEF38</i>		
chr5:779790-1797488	Signal 3	23	<i>CLPTM1L, TERT</i>		
	PP > 30%	7	<i>CLPTM1L, TERT</i>		
chr5:55531884-56587883	Signal 1	3	<i>MAP3K1</i>		
	Signal 3	21	<i>MAP3K1</i>		<i>MAP3K1</i>

	Signal 4	70	MAP3K1	
	Signal 5	4	MAP3K1	
	PP > 30%	5	MAP3K1	
chr5:90289470-91289470	Signal 1	88	ARRDC3	ARRDC3
chr5:131907058-132907058	Signal 1	117	AFF4, HSPA4, ZCCHC10	HSPA4
	PP > 30%	1	AFF4, HSPA4	
chr5:157730013-158744083	Signal 1	5	EBF1	
chr5:169091487-170091487	Signal 1	19	FOXI1	
chr6:13213099-14222523	Signal 1	51	NOL7, RANBP9, RP1-223E5.4	
chr6:20121238-21121238	Signal 1	52	CDKAL1	
chr6:28422437-29426220	Signal 1	36	TRIM27	
chr6:129849119-130849119	Signal 1	43		L3MBTL3
chr6:151418856-152937016	Signal 1	1	ESR1	
	Signal 3	1	ESR1	
	Signal 4	6	C6orf211, CCDC170, ESR1	
	Signal 5	173		ESR1
	Signal 6	22	CCDC170, ESR1	ESR1 ESR1
	PP > 30%	4	ESR1	
chr7:91130620-92181597	Signal 1	318	KRIT1	AKAP9
chr7:101054599-102054599	Signal 1	6	CUX1	CUX1
chr8:29009616-30009616	Signal 1	16	DUSP4	
chr8:101978959-102978959	Signal 1	47	GRHL2, KB-1562D12.1, KB-1930G5.4	
	PP > 30%	2	KB-1930G5.4	
chr8:116709548-117709548	Signal 1	164	TRPS1	
chr8:124110166-125110166	Signal 1	23	FBXO32	
	Signal 2	6	FBXO32	
	PP > 30%	1	FBXO32, WDYHV1	
chr8:127424659-130041931	Signal 2	44	MYC	
	PP > 30%	5	MYC	
chr9:109803808-111395353	Signal 4	1	KLF4	
	PP > 30%	6	KLF4	
chr10:8588113-9588113	Signal 1	49	GATA3	
	PP > 30%	1	GATA3	
chr10:21532942-22909392	Signal 2	58	BMI1, COMMD3	
chr10:80341148-81387721	Signal 1	10	ZMIZ1	
	Signal 3	9	ZCCHC24	
	PP > 30%	2	ZMIZ1	
chr10:114273927-115286154	Signal 2	42	TCF7L2	
chr10:122593901-123849324	Signal 1	1	FGFR2	
	Signal 2	7	FGFR2	
	Signal 3	1		FGFR2
	Signal 4	3		FGFR2
	Signal 5	1	FGFR2	
	PP > 30%	6	FGFR2	FGFR2

chr11:303017-1303017	Signal 1	19	<i>CD151, EPS8L2, PDDC1</i>	<i>PIDD1</i>
chr11:65043827-66083066	Signal 1	13	<i>AP5B1, CFL1, OVOL1, RNASEH2C</i>	
chr11:68831418-69879161	Signal 1	1	<i>CCND1, MYEOV</i>	
	Signal 2	3	<i>CCND1, MYEOV</i>	
	Signal 3	20	<i>CCND1, MYEOV</i>	
	PP > 30%	5	<i>CCND1, MYEOV</i>	
chr11:107845515-108857137	Signal 1	59	<i>C11orf65, KDELC2</i>	<i>ATM</i>
	CIMBA	8		<i>ATM</i>
chr12:13913931-14913931	Signal 1	18	<i>ATF7IP</i>	
chr12:27639846-29034415	Signal 2	375	<i>CCDC91, PTHLH</i>	
chr12:95527759-96527759	Signal 1	2	<i>NTN4</i>	
	PP > 30%	1	<i>NTN4</i>	
chr12:115336522-116336522	Signal 1	7	<i>TBX3</i>	
	Signal 2	1	<i>TBX3</i>	
	Signal 3	8	<i>TBX3</i>	
	PP > 30%	7	<i>TBX3</i>	
chr12:120332146-121332146	Signal 1	5	<i>MSI1, RPLP0</i>	
	PP > 30%	1	<i>RPLP0</i>	
chr13:32468810-33472626	Signal 1	5		<i>BRCA2</i>
chr14:36632769-37635752	Signal 1	19	<i>PAX9, SLC25A21</i>	
	PP > 30%	3	<i>PAX9</i>	
chr14:68117194-69534682	Signal 1	8	<i>ZFP36L1</i>	
	Signal 2	4	<i>ZFP36L1</i>	
	PP > 30%	3	<i>ZFP36L1</i>	
chr14:92604072-93616351	Signal 1	34		<i>RIN3</i>
chr15:91009215-92009215	Signal 1	22	<i>RCCD1</i>	
chr16:3606788-4606788	Signal 1	23	<i>ADCY9, CREBBP</i>	
chr16:52038825-53038825	Signal 1	1	<i>TOX3</i>	
	PP > 30%	2	<i>TOX3</i>	
chr16:53300954-54355291	Signal 1	6	<i>CTD-3032H12.2, FTO, IRX3</i>	
chr16:54182064-55182064	Signal 1	3	<i>CRNDE</i>	
chr16:80148327-81150805	Signal 1	14	<i>CDYL2, DYNLRB2, RP11-18F14.4, RP11-525K10.3</i>	
	PP > 30%	1	<i>DYNLRB2</i>	
chr17:77281387-78281725	Signal 1	10	<i>CCDC40</i>	
chr18:23832476-25075396	Signal 3	31	<i>KCTD1</i>	
	PP > 30%	6	<i>KCTD1</i>	
chr18:41899590-42899590	Signal 1	38	<i>SETBP1</i>	<i>SETBP1</i>
chr19:12658277-14454571	Signal 1	21	<i>DAND5, GCDH, HOOK2, JUNB, MAST1, PRDX2</i>	
chr19:16795023-17894124	Signal 1	16	<i>ABHD8, MRPL34</i>	
	CIMBA	10	<i>ABHD8, MRPL34</i>	<i>ANKLE1</i>
chr19:18050434-19071141	Signal 1	56	<i>CRLF1, ELL, FKBP8, GDF15, ISYNA1, KXD1, UBA52</i>	
chr19:19048246-20048246	Signal 1	162	<i>ATP13A1, GATAD2A, LPAR2, MAU2, MEF2B, MEF2BNB, NDUFA13, PBX4, RFXANK, SUGP1</i>	<i>GATAD2A</i>
chr19:29777729-30777729	Signal 1	60	<i>CCNE1</i>	

chr19:43783447-44786513	Signal 1	10	KCNN4, PLAUR, SMG9			
chr21:16073983-17073983	Signal 1	7	NRIP1			
	PP > 30%	5	NRIP1			
chr22:28000000-30121477	Signal 1	3	CHEK2			
	Signal 2	2	CHEK2			
	Signal 3	59	CHEK2, CTA-292E10.6, EWSR1, XBP1	CHEK2	CHEK2	
	PP > 30%	3	CHEK2, XBP1			
chr22:38068833-39859355	Signal 1	27	MAFF, PLA2G6, TMEM184B			
	Signal 3	4	CBX6, NPTXR, SUN2			
chr22:40376234-41527870	Signal 1	196	MKL1, SLC25A17			
chr22:41538786-42538786	Signal 1	10	EP300			
chr22:45783297-46783297	Signal 1	34	WNT7B			

^a GRCh37/hg19, bp

^b Independent signal or set of variants with PP $\geq$ 30%

^c Number of CCV or number of variants with PP $\geq$ 30%

High confidence target genes by ^d distal regulatory, ^e promoter, or ^f coding variants at the signal or at the set of variants with PP $\geq$ 30%