A transcriptome-wide association study of 229,000 women identifies new candidate susceptibility genes for breast cancer

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Abstract:

Breast cancer risk variants identified in genome-wide association studies explain only a small fraction of familial relative risk, and genes responsible for these associations remain largely unknown. To identify novel risk loci and likely causal genes, we performed a transcriptome-wide association study evaluating associations of genetically predicted gene expression with breast cancer risk in 122,977 cases and 105,974 controls of European ancestry. We used data from the Genotype-Tissue Expression Project to establish genetic models to predict gene expression in breast tissue and evaluated model performance using data from The Cancer Genome Atlas. Of the 8,597 genes evaluated, significant associations were identified for 48 at a Bonferroni-corrected threshold of $P < 5.82\times10^{-6}$, including 14 genes at loci not yet reported for breast cancer. We silenced 13 genes and showed an effect for 11 on cell proliferation and/or colony forming efficiency. Our study provides new insights into breast cancer genetics and biology.

Breast cancer is the most common malignancy among women in many countries[1]. Genetic factors play an important role in its etiology. Since 2007, genome-wide association studies (GWAS) have identified approximately 170 genetic loci harboring common, low-penetrance variants for breast cancer[6-13], but these variants explain less than 20% of familial relative risk[7]. Most disease-associated risk variants identified by GWAS are located in non-protein coding regions and are not in linkage disequilibrium (LD) with any nonsynonymous coding single nucleotide polymorphisms (SNPs)[14]. Many of these susceptibility variants are located in gene regulatory elements[15,16], and it has been hypothesized that many GWAS-identified associations may be driven by the regulatory function of risk variants on the expression of nearby genes. For breast cancer, recent studies have already shown that GWAS-identified associations at more than 15 loci are likely due to the effect of risk variants at these loci on regulating the expression of either nearby or more distal genes[7,9,10,13,17-22]. However, for the large majority of the GWAS-identified breast cancer risk loci, the genes responsible for the associations remain unknown.

Several studies have reported that regulatory variants may account for a large proportion of disease heritability not yet discovered through GWAS[23-25]. Many of these variants may have a small effect size, and thus are difficult to identify in individual SNP-based GWAS, even with a large sample size. Applying gene-based approaches that aggregate the effects of multiple variants into a single testing unit may increase study power to identify novel disease-associated loci. Transcriptome-wide association studies (TWAS) systematically investigate the association of genetically predicted gene expression with disease risk, providing an effective approach to identify novel susceptibility genes[26-29]. Recently, Hoffman et al performed a TWAS including 15,440 cases and 31,159 controls and reported significant associations for five genes with breast

cancer risk[30]. However, the sample size of that study was relatively small and several reported associations were not significant after Bonferroni correction. Herein, we report results from a larger TWAS of breast cancer that used the MetaXcan method[26] to analyze summary statistics data from 122,977 cases and 105,974 controls of European descent from the Breast Cancer Association Consortium (BCAC).

Results

Gene expression prediction models

The study design is shown in **Supplementary Figure 1**. We used transcriptome and genotyping data from 67 women of European descent included in the Genotype-Tissue Expression (GTEx) project to build genetic models to predict RNA expression levels for each gene expressed in normal breast tissues, by applying the elastic net method (α=0.5) with ten-fold cross-validation. Genetically regulated expression was estimated using variants within a 2 MB window flanking the respective gene boundaries, inclusive. SNPs with a minor allele frequency of at least 0.05 and included in the HapMap Phase 2 were used for model building. Of the models built for 12,696 genes, 9,109 showed a prediction performance (R^2) of at least 0.01 ($\geq$10% correlation between predicted and observed expression). For genes for which the expression could not be predicted well using this approach, we built models using only SNPs located in the promoter or enhancer regions, as predicted using three breast cell lines in the Roadmap Epigenomics Project/Encyclopedia of DNA Elements Project. This approach leverages information from functional genomics and reduces the number of variants for variable selection, therefore potentially improving statistical power. This enabled us to build genetic models for additional 3,715 genes with $R^2 \geq 0.01$. **Supplementary Table 1** provides detailed information regarding the

performance threshold and types of models built. Overall, genes that were predicted with $R^2 \geq 0.01$ in GTEx data were also predicted well in The Cancer Genome Atlas (TCGA) tumor-adjacent normal tissue data (correlation coefficient of 0.55 for R^2 in two datasets; **Supplementary Figure 2**). Based on model performance in GTEx and TCGA, we prioritized 8,597 genes for analyses of the associations between predicted gene expression and breast cancer risk using the following criteria: 1) genes with a model prediction $R^2 \geq 0.01$ in the GTEx set (10% correlation) and a Spearman's correlation coefficient of ≥ 0.1 in the external validation experiment, 2) genes with a prediction $R^2 \geq 0.09$ (30% correlation) in the GTEx set regardless of their performance in the TCGA set, 3) genes with a prediction $R^2 \geq 0.01$ in the GTEx set (10% correlation) that could not be evaluated in the TCGA set because of a lack of data.

Associations of predicted expression with breast cancer

Using the MetaXcan method[26], we performed association analyses to evaluate predicted gene expression and breast cancer risk using the meta-analysis summary statistics of SNPs generated for 122,977 cases and 105,974 controls of European ancestry included in BCAC. For the majority of the tested genes, most of the SNPs selected for prediction models were used for the association analyses (e.g., ≥80% predicting SNPs used for 95.6% of the tested genes). Lambda 1,000 ($\lambda_{1,000}$), a standardized estimate of the genomic inflation scaling to a study of 1,000 cases and 1,000 controls, was 1.004 in our study (Quantile-quantile (QQ) plot presented in **Supplementary Figure 3 (a)**). Of the 8,597 genes evaluated, we identified 179 whose predicted expression was associated with breast cancer risk at $P<1.05\times10^{-3}$, a FDR-corrected significance level (**Figure 1**, **Supplementary Table 2**). Of these, 48 showed a significant association at the Bonferroni-corrected threshold of $P\leq5.82\times10^{-6}$ (**Figure 1**, **Tables 1-3**), including 14 genes

located at 11 loci that are 500 kb away from any risk variant identified in previous GWAS (**Table 1**). An association between lower predicted expression and increased breast cancer risk was detected for *LRRC3B* (3p24.1), *SPATA18* (4q12), *UBD* (6p22.1), *MIR31HG* (9p21.3), *RIC8A* (11p15.5), *B3GNT1* (11q13.2), *GALNT16* (14q24.1) and *MAN2C1* and *CTD-2323K18.1* (15q24.2). Conversely, an association between higher predicted expression and increased breast cancer risk was identified for *ZSWIM5* (1p34.1), *KLHDC10* (7q32.2), *RP11-867G23.10* (11q13.2), *RP11-218M22.1* (12p13.33) and *PLEKHD1* (14q24.1). The remaining 34 associated genes are located at known breast cancer susceptibility loci (**Tables 2-3**). Among them, 23 have not yet been implicated as genes responsible for association signals identified at these loci through expression quantitative trait loci (eQTL) and/or functional studies, and do not harbor GWAS or fine-mapping identified risk variants (**Table 2**), while the other eleven (*KLHDC7A*[7], *ALS2CR12*[31], *CASP8*[31,32], *ATG10*[9], *SNX32*[33], *STXBP4*[34,35] , *ZNF404*[8], *ATP6AP1L*[9], *RMND1*[17], *L3MBTL3*[6], and *RCCD1*[10]) had been reported as potential causal genes at breast cancer susceptibility loci or harbor GWAS or fine-mapping identified risk variants (**Table 3**). Except for *RP11-73O6.3* and *L3MBTL3*, there was no evidence of heterogeneity (I^2<0.2) across the iCOGS, OncoArray, and GWAS datasets included in our analyses (**Supplementary Table 3**). Overall, we identified 37 novel susceptibility genes for breast cancer and confirmed eleven genes known to potentially play a role in breast cancer susceptibility.

To determine whether the associations between predicted gene expression and breast cancer risk were independent of GWAS-identified association signals, we performed conditional analyses adjusting for the GWAS-identified risk SNPs closest to the TWAS-identified gene (**Supplementary Table 4**)[36]. We found that the associations for 11 genes (*LRRC3B*, *SPATA18*,

KLHDC10, *MIR31HG*, *RIC8A*, *B3GNT1*, *RP11-218M22.1*, *MAN2C1*, *CTD-2323K18.1* **(Table 1)**, *ALK*, *CTD-3051D23.1* **(Table 2)**) remained statistically significant at $P<5.82\times10^{-6}$ (**Tables 1-3**). This suggests the expression of these genes may be associated with breast cancer risk independent of the GWAS-identified risk variant(s). For nine of the genes (*SPATA18*, *KLHDC10*, *MIR31HG*, *RIC8A*, *RP11-218M22.1*, *MAN2C1*, *CTD-2323K18.1* **(Table 1)**, *ALK*, and *CTD-3051D23.1* **(Table 2)**), the significance of the association remained essentially unchanged, suggesting these associations may be entirely independent of GWAS-identified association signals.

Of the 131 genes showing an association at $5.82\times10^{-6} < P <1.05\times10^{-3}$ (significant after FDR-correction but not Bonferroni-correction), 38 are located at GWAS-identified risk loci (**Table 4**). Except for *RP11-400F19.8*, there was no evidence of heterogeneity in TWAS association ($I^2<0.2$) across the iCOGS, OncoArray, and GWAS studies (**Supplementary Table 3**). After adjusting for the risk SNPs, associations for *MTHFD1L*, *PVT1*, *RP11-123K19.1*, *FES*, *RP11-400F19.8*, *CTD-2538G9.5*, and *CTD-3216D2.5* remained significant at $p\leq1.05\times10^{-3}$, again suggesting that the association of these genes with breast cancer risk may be independent of the GWAS-identified association signals (**Table 4**).

For 41 of the 48 associated genes that reached the Bonferroni-corrected significant level, we obtained individual-level data from subjects included in the iCOGS (n=84,740) and OncoArray (n=112,133) datasets, which was 86% of the subjects included in the analysis using summary statistics (**Supplementary Table 5**). The results from the analysis using individual-level data were very similar to those described above using MetaXcan analyses (Pearson correlation of z-

scores was 0.991 for iCOGS data and 0.994 for OncoArray data), although not all associations reached the Bonferroni-corrected significant level, possibly due to a smaller sample size (**Supplementary Table 5**). Conditional analyses using individual level data also revealed consistent results compared with analyses using summary data. We found that for several genes within the same genomic region, their predicted expression was correlated with each other (**Tables 1-3**). The associations between predicted expression of *PLEKHD1* and *ZSWIM5* and breast cancer risk were largely influenced by their corresponding closest risk variants identified in GWAS, although these risk variants are >500 kb away from these genes (**Table 1**). There were significant correlation of rs999737 and rs1707302 with genetically predicted expression of *PLEKHD1* (r = -0.47 in OncoArray dataset and -0.48 in iCOGS dataset) and *ZSWIM5* (r = 0.50 in OncoArray dataset and 0.51 in iCOGS dataset), respectively.

INQUISIT algorithm scores

For the 48 associated genes after Bonferroni correction, we assessed their integrated expression quantitative trait and *in silico* prediction of GWAS target **(**INQUISIT) scores[7] to assess whether there are other evidence beyond the scope of eQTL for supporting our TWAS-identified genes as candidate target genes at GWAS-identified loci. The detailed methodology for INQUISIT scores have been described elsewhere[7]. In brief, a score for each gene-SNP pair is calculated across categories representing potential regulatory mechanisms - distal or proximal gene regulation (promoter). Features contributing to the score are based on functionally important genomic annotations such as chromatin interactions, transcription factor binding, and eQTLs. Compared with evidence from eQTL only, INQUISIT scores incorporate additional lines of evidence, including distal regulations. The INQUISIT scores for our identified genes are shown in

Supplementary Table 6. Except for *UBD* with a very low score in the distal regulation category (0.05), none of the genes at novel loci (**Table 1**) showed evidence to be potential target genes for GWAS-identified breast cancer susceptibility loci. This is interesting and within the expectation since these genes may represent novel association signals. There was evidence suggesting that *RP11-439A17.7, NUDT17, ANKRD34A, BTN3A2, AP006621.6, RPLP2, LRRC37A2, LRRC37A, KANSL1-AS1, CRHR1* and *HAPLN4* listed in Table 2, and all eleven genes listed in Table 3, may be target genes for risk variants at these loci (**Supplementary Table 6**). For *NUDT17, ANKRD34A, RPLP2, LRRC37A2, LRRC37A, KANSL1-AS1, CRHR1, HAPLN4, KLHDC7A, ALS2CR12, CASP8, ATG10, ATP6AP1L, L3MBTL3, RMND1, SNX32, RCCD1, STXBP4* and *ZNF404*, the INQUISIT scores were not derived only from eQTL data, providing orthogonal support for these genes. For these loci, the associations of candidate causal SNPs with breast cancer risk may be mediated through these genes. This is in general consistent with the findings from the conditional analyses.

Pathway enrichment analyses

Ingenuity Pathway Analysis (IPA)[37] suggested potential enrichment of cancer-related functions for the identified protein-coding genes (**Supplementary Table 7**). The top canonical pathways identified included apoptosis related pathways (Granzyme B signaling (p=0.024) and cytotoxic T lymphocyte-mediated apoptosis of target cells (p=0.046)), immune system pathway (inflammasome pathway (p=0.030)), and tumoricidal function of hepatic natural killer cells (p=0.036). The identified pathways are largely consistent with previous findings [7]. For the associated lncRNAs, pathway analysis of their highly co-expressed protein-coding genes also revealed potential over-representation of cancer-related functions (**Supplementary Table 7**).

***In vitro* assays of gene functions**

To assess the function of genes whose high predicted expression were associated with increased breast cancer risk, we selected 13 genes for knockdown experiments in breast cells: *ZSWIM5*, *KLHDC10*, *RP11-218M22.1* and *PLEKHD1* (**Table 1**), *UBLCP1*, *AP006621.6*, *RP11-467J12.4*, *CTD-3032H12.1* and *RP11-15A1.7* (**Table 2**), and *ALS2CR12*, *RMND1*, *STXBP4* and *ZNF404* (**Table 3**). As negative controls, we selected *B2M*, *ARHGDIA* and *ZAP70* using the criteria: 1) ≥2 MB from any known breast cancer risk locus; 2) not an essential gene in breast cancer[38,39]; and 3) not predicted to be a target gene in INQUISIT. In addition, as positive controls, we included *PIDD1* (**Table 4**)[7], *NRBF2*[20] and *ABHD8*[22], which have been functionally validated as target genes at breast cancer risk loci. We performed quantitative PCR (qPCR) on a panel of three 'normal' mammary epithelial and 15 breast cancer cell lines to analyze their expression levels (**Supplementary Figure 4 and Supplementary Table 8**). All 19 genes were expressed in the normal mammary epithelial line 184A1[40] and the luminal breast cancer cell lines, MCF7 and T47D, so we used these cell lines for the proliferation assay, and MCF7 for the colony formation assay[41]. We also evaluated *SNX32*, *ALK* and *BTN3A2* by qPCR, but they were not expressed in T47D and MCF7 cells; therefore they were not evaluated further. It was difficult to design siRNAs against *RP11-867G23.1* and *RP11-53O19.1* because they both have multiple transcripts with limited, GC-rich regions in common. We did not include *RPLP2* because it is already known to be an essential gene for breast cancer survival[42]. Knockdown of the 19 tested genes was achieved by small short interfering RNA (siRNA) (**Supplementary Table 9**) and the knockdown efficiency was calculated in 184A1, MCF7 and T47D for each siRNA pair. Robust

knockdown of the gene of interests (GOI) was validated by qPCR with the majority of the siRNAs (**Supplementary Figure 5**).

To evaluate the survival and proliferation ability of cells following gene interruption, we used an IncuCyte to quantify cell proliferation in real time and quantified the corrected proliferation of cells with knocking down of GOI in comparison to that of cells with non-target control (NTC) siRNA). As expected, knockdown of the three negative control genes (*B2M*, *ARHGDIA* and *ZAP70*) did not significantly change cell proliferation in any of the three cell lines (**Figure 2**A**, Supplementary Figure 6)**. However, with the exception of *UBLCP1*, *RMND1* and *STXBP4*, knockdown of all other genes (11 TWAS-identified genes along with two known genes, *ABHD8* and *NRBF2*) resulted in significantly decreased cell proliferation in 184A1 normal breast cells, with *KLHDC10, PLEKHD1, RP11-218M22.1, AP006621.6, ZNF404, RP11-467J12.4, CTD-3032H12.1* and *STXBP4* showing a similar effect in one or both cancer cell lines. Down-regulation of three lncRNAs (*RP11-218M22.1*, *RP11-467J12.4* and *CTD-3032H12.1)* resulted in significant reduction in cell proliferation in all three cell lines. We also evaluated the effect of inhibition of these genes on colony forming ability in MCF7 cells. Knockdown of the three negative control genes did not significantly affect colony forming efficiency (CFE). By contrast, knockdown of *PIDD1, RP11-15A1.7, RP11-218M22.1, AP006621.6, ZNF404, RP11-467J12.4* and *CTD-3032H12.1* resulted in significantly decreased CFE in MCF7 cells compared to the NTC (**Figure 2B, Supplementary Figure 7).**

Discussion

This is the largest study to systematically evaluate associations of genetically predicted gene

expression across the human transcriptome with breast cancer risk. We identified 179 genes showing a significant association at the FDR-corrected significance level. Of these, 48 genes showed an association at the Bonferroni-corrected threshold, including 14 at genomic loci that have not previously been implicated for breast cancer risk. Of the 34 genes located at known risk loci, 23 have not previously been shown to be the targets of GWAS-identified risk SNPs at corresponding loci and not harbor any risk SNPs. Our study provides substantial new information to improve the understanding of genetics and etiology for breast cancer.

It is possible that TWAS-identified genes may be associated with breast cancer through their correlation with disease causal genes. To determine the potential functional significance of TWAS-identified genes and provide evidence for causal inference, we knocked down 13 genes for which high predicted levels of expression were associated with an increased breast cancer risk, in one normal and two breast cancer cell lines, and measured the effect on proliferation and CFE. Although there was some variation between cell lines, knockdown of 11 of the 13 genes showed an effect in at least one cell line, particularly on proliferation in 184A1 normal breast cells; the effects were strongest and most consistent for the lncRNAs, *RP11-218M22.1*, *RP11-467J12.4* and *CTD-3032H12.1*. The observation of a more consistent effect in the normal breast cell line compared with the cancer cell lines is not surprising as cancer cell lines have increased capacity to handle gene interference through mutations which enhance cell survival. Rewiring of pathways and compensatory mechanisms is a hallmark of cancer. Knockdown of *PIDD1, NRBF2* and *ABHD8*¸ for which breast cancer risk associated haplotypes have been shown to be associated with increased expression in reporter assays[7,20,22], affected either proliferation or colony forming efficiency, supporting the results from this study.

Some of the genes with strong functional evidence from our study have been reported to have important roles in carcinogenesis. For example, *RP11-467J12.4* (PR-lncRNA-1) is a p53-regulated lncRNA that modulates gene expression in response to DNA damage downstream of p53[43]. *STXBP4* encodes Syntaxin binding protein 4, a scaffold protein that can stabilise and prevent degradation of an isoform of p63, a member of the p53 tumor suppressor family[44]. *KLHDC10* encodes a member of the Kelch superfamily that can activate apoptosis signal-regulating kinase 1, contributing to oxidative stress-induced cell death[45]. Notably, another member of this superfamily, *KLHDC7A*, has recently been identified as the target gene at the 1p36 breast cancer risk locus[7].

SNX32, ALK and *BTN3A2* are also likely susceptibility genes for breast cancer risk. However, their low or absent expression in our chosen breast cell lines prevented further functional analysis. *ALK* (Anaplastic lymphoma kinase) copy number gain and overexpression have been reported in aggressive and metastatic breast cancers[46]. Therapeutic targeting of ALK rearrangement has significantly improved survival in advanced ALK-positive lung cancer[47], making it an attractive target for breast and other cancers. *BTN3A2* is a member of the B7/butyrophilin-like group of Ig superfamily receptors modulating the function of T-lymphocytes. Over-expression of *BTN3A2*in epithelial ovarian cancer is associated with higher infiltrating immune cells and a better prognosis[48].

Our analyses identified multiple genes with reduced expression associated with increased breast cancer risk. Among them, *LRRC3B* and *CASP8* are putative tumor suppressors in multiple cancers, including breast cancer. Leucine-rich repeat-containing 3B (*LRRC3B)* is a putative

LRR-containing transmembrane protein, which is frequently inactivated via promoter hypermethylation leading to inhibition of cancer cell growth, proliferation, and invasion[49]. *CASP8* encodes a member of the cysteine-aspartic acid protease family, which play a central role in cell apoptosis. Previous studies have suggested that caspase-8 may act as a tumor suppressor in certain types of lung cancer and neuroblastoma, although this function has not yet been demonstrated in breast cancer. Notably, several large association studies have identified SNPs at the 2q33/*CASP8* locus associated with increased breast cancer risk[31,50]. Consistent with our data, eQTL analyses showed that the risk alleles for breast cancer were associated with reduced *CASP8* mRNA levels in both peripheral blood lymphocytes and normal breast tissue[31].

For seven of the genes listed in Tables 1 and 2, we found some evidence from studies using tumor tissues, *in vitro* or *in vivo* experiments linking them to cancer risk (**Supplementary Table 10)**, although their association with breast cancer has not been demonstrated in human studies. For five of them, including *LRRC3B*, *SPATA18*, *RIC8A*, *ALK* and *CRHR1*, previous *in vitro* and *in vivo* experiments and human tissue studies showed a consistent direction of the association as demonstrated in our studies. For two other genes (*UBD* and *MIR31HG*), however, results from previous studies were inconsistent, reporting both potential promoting and inhibiting effects on breast cancer development. Future studies are needed to evaluate functions of these genes.

We included a large number of cases and controls, providing strong statistical power for the association analysis. This large sample size enabled us to identify a large number of candidate breast cancer susceptibility genes, much larger than the number identified in a TWAS study with a sample size of about 20% of ours[30]. The previous study included subjects of different races,

which could affect the results as linkage disequilibrium (LD) patterns differ by races. Of the five genes reported in that smaller TWAS that showed a suggestive association with breast cancer risk, the association for the *RCCD1* gene was replicated in our study **(Table 3)**. The other four genes (*ANKLE1*, *DHODH*, *ACAP1* and *LRRC25)* were not evaluated in our study because of unsatisfactory performance of our breast specific models for these genes which were built using the GTEx reference dataset including only female European descendants.

A substantial proportion of SNPs included in the OncoArray and iCOGS were selected from breast cancer GWAS and fine-mapping analyses, and thus these arrays were enriched for association signals with breast cancer risk. As a result, the overall λ value for the BCAC association analyses of individual variants is 1.26 after adjusting for population stratifications (QQ plot in **Supplementary Figure 3 (b)**)[7]. The λ value for the associations of the ~257,000 SNPs included in the gene expression prediction models of the 8,597 genes tested in our association analysis is 1.40 (QQ plot in **Supplementary Figure 3 (c)**). This higher λ value is perhaps expected because of a potential further enrichment of breast cancer associated signals in the set of SNPs selected to predict gene expression. There could be additional gain of power (and thus a higher λ value) in TWAS as it aggregates the effect of multiple SNPs to predict gene expression and use genes as the unit for association analyses. The lambda (λ) for our associated analyses of 8,597 genes was 1.51 (QQ plot presented in **Supplementary Figure 3 (a)**) likely due to the potential enrichment and power gain as well as our large sample size, and the highly polygenic nature of the disease[7,51]. Interestingly, high λ values were also found in recent large studies of other polygenic traits, such as body mass index (BMI) (λ = 1.99) and height (λ =

2.7)[52,53]. The $\lambda_{1,000}$, a standardized estimate of the genomic inflation scaling to a study of 1,000 cases and 1,000 controls, is 1.004 in our study.

The statistical power of our study is very high to detect associations for genes with a relatively high cis-heritability (h^2) (**Supplementary Figure 8)**. For example, our study has 80% statistical power to detect an association with breast cancer risk at $P<5.82\times10^{-6}$ with an OR of 1.07 or higher per one standard deviation increase (or decrease) in the expression level of genes with an h^2 of 0.1 or higher. One limitation of our study is the small sample size for building gene expression prediction models, which may have affected the precision of model parameter estimates. We expect that models built with a larger sample size will identify additional association signals. We used samples from women of European origin in model building, given differences in gene expression patterns between males and females and in genetic architecture across ethnicities[54]. We also used gene expression data of tumor-adjacent normal tissue samples from European descendants in TCGA as an external validation step to prioritize genes for association analyses. Given potential somatic alterations in tumor-adjacent normal tissues, we retained all models showing a prediction R^2 of at least 0.09 in GTEx, regardless of their performance in TCGA. Not all genes have a significant hereditary component in expression regulation, and thus these genes could not be investigated in our study. For example, previous studies have provided strong evidence to support a significant role of the *TERT*, *ESR1*, *CCND1*, *IGFBP5*, *TET2* and *MRPS30* genes in the etiology of breast cancer. However, expression of these genes cannot be predicted well using the data from female European descendants included in the GTEx and thus they were not included in our association analyses. **Supplementary Table**

11 summarizes the performance of prediction models and association results for breast cancer target genes reported previously at GWAS-identified loci.

In summary, our study has identified multiple gene candidates that can be further functionally characterized. The silencing experiments we performed suggest that many of the genes identified are likely to mediate risk of breast cancer by affecting proliferation or CFE, two hallmarks of cancer. Further investigation of genes identified in our study will provide additional insight into the biology and genetics of breast cancer.

URLs. GTEx protocol, http://www.gtexportal.org/home/documentationPage; Gencode V19 annotation file, http://www.gencodegenes.org/releases/19.html; HaploReg, http://archive.broadinstitute.org/mammals/haploreg/data/; OncoArray, http://epi.grants.cancer.gov/oncoarray/;

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Author Contributions

W.Z. and J.L. conceived the study. L.W. contributed to the study design, and performed statistical analyses. L.W., W.Z. and G.C.-T. wrote the manuscript with significant contributions from W.S., J.L., X.G., and S.L.E.. W.S. performed the *in vitro* experiments. G.C.-T. directed the *in vitro* experiments. X.G. contributed to the model building and pathway analyses. J.B. contributed to the bioinformatics analyses. F.A.-E., E.R., and S.L.E. contributed to the *in vitro* experiments. Y. L. and C. Z. contributed to the model building. K.M., M.K.B., X.-O.S., Q.W., J.D., B.L., C.Z., H.F., A.G., R.T.B., A.M.D., P.D.P.P., J.S., R.L.M., P.K., and D.F.E, contributed to manuscript revision, statistical analyses and/or BCAC data management. I.L.A., H.A.-C., V.A., K.J.A., P.L.A., M. Barrdahl, C.B., M.W.B., J.B., M. Bermisheva, C.B., N.V.B., S.E.B., H. Brauch, H. Brenner, L.B., P.B., S.Y.B., B.B., Q.C., T.C., F.C., B.D.C., J.E.C., J.C.-C., X.C., T.-Y.D.C., H.C., C.L.C., NBCS Collaborators, M.C., S.C., F.J.C., D.C., A.C., S.S.C., J.M.C., K.C., M.B.D., P.D., K.F.D., T.D., I.d.S.S., M. Dumont, M. Dwek, D.M.E., U.E., H.E., C.E., M.E., L.F., P.A.F., J.F., D.F.-J., O.F., H.F., L.F., M. Gabrielson, M.G.-D., S.M.G., M.G.-C., M.M.G., M. Ghoussaini, G.G.G., M.S.G., D.E.G., A.G.-N., P.G., E. Hahnen, C.A.H., N.H., P. Hall, E. Hallberg, U.H., P. Harrington, A. Hein, B.H., P. Hillemanns, A. Hollestelle, R.N.H., J.L.H., G.H., K.H., D.J.H., A.J., W.J., E.M.J., N.J., K.J., M.E.J., A. Jung, R.K., M.J.K., E.K., V.-M.K., V.N.K., D.L., L.L.M., J. Li, S.L., J. Lissowska, W.-Y.L., S.Loibl, J.L., C.L., M.P.L., R.J.M., T.M., I.M.K., A. Mannermaa, J.E.M., S.M., D.M., H.M.-H., A. Meindl, U.M., J.M., A.M.M., S.L.N., H.N., P.N., S.F.N., B.G.N., O.I.O., J.E.O., H.O., P.P., J.P., D.P.-K., R.P., N.P., K.P., B.R., P.R., N.R., G.R., H.S.R., V.R., A. Romero, J.R., A. Rudolph, E.S., D.P.S, E.J.S., M.K.S., R.K.S., A.S., R.J.S., C. Scott, S.S., M.S., M.J.S., A.S., M.C.S., J.J.S., J.S., H.S., A.J.S., R.T.,

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Competing financial interests

The authors declare no competing financial interests.

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Figure Legends

Figure 1. Manhattan plot of association results from the breast cancer transcriptome-wide association study. Results are based on 122,977 cases and 105,974 controls. The red line represents $P = 5.82 \times 10^{-6}$. The blue line represents $P = 1.00 \times 10^{-3}$.

Figure 2. Heat maps of proliferation and colony formation efficiency in breast cells. (a) Proliferation efficiency. **(b)** colony formation efficiency. Error bars, SD (N=2). P-values were determined by one-way ANOVA followed by Dunnett's multiple comparisons test: *P-value < 0.05. NTC: non-target control.

Table 1. Fourteen expression-trait associations for genes located at genomic loci at least 500 kb away from any GWAS-identified breast cancer risk variants

Region	Gene[a]	Type[b]	Z score	*P* value[c]	R^{2c}	Closest risk SNP[d]	Distance to the closest risk SNP (kb)	*P* value after adjusting for adjacent risk SNPs[e]
1p34.1	***ZSWIM5***	Protein	5.26	1.43×10^{-7}	0.17	rs1707302	829	0.006
3p24.1	*LRRC3B*	Protein	-9.57	1.11×10^{-21}	0.17	rs653465	591	1.60×10^{-6}
4q12	*SPATA18*	Protein	-4.62	3.86×10^{-6}	0.11	rs6815814	14,101	3.98×10^{-6}
6p22.1	*UBD*	Protein	-4.87	1.10×10^{-6}	0.13	rs9257408	597	0.94
7q32.2	***KLHDC10***	Protein	5.21	1.92×10^{-7}	0.14	rs4593472	892	2.90×10^{-7}
9p21.3	*MIR31HG*	lncRNA	-5.02	5.22×10^{-7}	0.12	rs1011970	502	1.23×10^{-7}
11p15.5	*RIC8A*	Protein	-5.27	1.40×10^{-7}	0.15	rs6597981	588	4.95×10^{-6}
11q13.2	*B3GNT1*	Protein	-5.85	4.88×10^{-9}	0.09	rs3903072	530	3.50×10^{-6}
11q13.2	*RP11-867G23.10*	transcript	4.71	2.49×10^{-6}	0.03	rs3903072	594	2.61×10^{-4}
12p13.33	***RP11-218M22.1***	lncRNA	5.02	5.27×10^{-7}	0.19	rs12422552	13,641	5.17×10^{-7}
14q24.1	*GALNT16*	Protein	-8.27	1.38×10^{-16}	0.04	rs999737	691	8.57×10^{-4}
14q24.1	***PLEKHD1***	Protein	7.50	6.55×10^{-14}	0.02	rs999737	917	0.12
15q24.2	*MAN2C1* [f]	Protein	-5.32	1.02×10^{-7}	0.39	rs2290203	15,851	9.56×10^{-8}
15q24.2	*CTD-2323K18.1* [f]	lncRNA	-4.65	3.27×10^{-6}	0.07	rs2290203	15,619	3.16×10^{-6}

[a] Genes that were siRNA-silenced for functional assays are bolded; SNPs used to predict gene expression are listed in the Supplementary Table 13

[b] Protein: protein coding genes; lncRNA: long non-coding RNAs; transcript: processed transcript

[c] *P* value: derived from association analyses of 122,977 cases and 105,974 controls; associations with $p \leq 5.82 \times 10^{-6}$ considered statistically significant based on Bonferroni correction of 8,597 tests (0.05/8,597); R^2: prediction performance (R^2) derived using GTEx data.

[d] Risk SNPs identified in previous GWAS or fine-mapping studies. The risk SNP closest to the gene is presented. A full list of all risk SNPs, and their distances to the genes are presented in the **Supplementary Table 4**

[e] Use of COJO method[36]

[f] Predicted expression of *MAN2C1* and *CTD-2323K18.1* was correlated (spearman R=0.76)

Table 2. Twenty-three expression-trait associations for genes located at genomic loci within 500 kb of any previous GWAS-identified breast cancer risk variants but not yet implicated as target genes of risk variants[#]

Region	Gene[a]	Type[b]	Z score	*P* value[c]	R^{2c}	Closest risk SNP[d]	Distance to the closest risk SNP (kb)	*P* value after adjusting for adjacent risk SNPs[e]
1p11.2	*RP11-439A17.7*	lncRNA	-5.34	9.07×10^{-8}	0.22	rs11249433	442	0.02
1q21.1	*NUDT17*	Protein	-6.27	3.58×10^{-10}	0.01	rs12405132	56	0.08
1q21.1	*ANKRD34A*	Protein	-5.05	4.42×10^{-7}	0.01	rs12405132	169	4.28×10^{-5}
2p23.1-2p23.2	*ALK*	Protein	4.67	3.06×10^{-6}	0.06	rs4577244	295	2.70×10^{-6}
3p21.31	*PRSS46*	Protein	-5.83	5.68×10^{-9}	0.13	rs6796502	89	0.002
3q12.2	*RP11-114I8.4*	lncRNA	-5.84	5.19×10^{-9}	0.02	rs9833888	356	0.09
5p12	*RP11-53O19.1*	lncRNA	10.38	2.94×10^{-25}	0.03	rs10941679	39	7.46×10^{-4}
5q33.3	***UBLCP1***	Protein	5.93	3.04×10^{-9}	0.07	rs1432679	446	0.37
5q33.3	*RP11-32D16.1*	lncRNA	-5.41	6.37×10^{-8}	0.09	rs1432679	283	1.32×10^{-4}
6p22.2	*BTN3A2*	Protein	4.61	3.97×10^{-6}	0.28	rs71557345	229	0.72
6q23.1	*RP11-73O6.3* [f]	lncRNA	-6.61	3.74×10^{-11}	0.11	rs6569648	105	0.41
11p15.5	***AP006621.6*** [g]	lncRNA	5.61	2.01×10^{-8}	0.34	rs6597981	21	0.52
11p15.5	*RPLP2* [g]	Protein	4.64	3.46×10^{-6}	0.27	rs6597981	7	0.51
14q32.33	*CTD-3051D23.1*	lncRNA	-5.06	4.21×10^{-7}	0.05	rs10623258	97	7.05×10^{-7}
16q12.2	***RP11-467J12.4***	lncRNA	8.04	9.02×10^{-16}	0.23	rs3112612	434	0.79
16q12.2	***CTD-3032H12.1***	lncRNA	4.92	8.58×10^{-7}	0.03	rs28539243	290	0.006
17q21.31	*LRRC37A* [g]	Protein	-5.89	3.85×10^{-9}	0.43	rs2532263	118	0.79
17q21.31	*KANSL1-AS1* [g]	lncRNA	-5.58	2.44×10^{-8}	0.62	rs2532263	18	0.95
17q21.31	*CRHR1* [g]	Protein	-5.29	1.22×10^{-7}	0.22	rs2532263	339	0.99
17q21.31	*LINC00671*	lncRNA	-5.85	4.95×10^{-9}	0.07	rs72826962	190	0.26
17q21.31	*LRRC37A2*	Protein	-5.77	7.93×10^{-9}	0.46	rs2532263	336	0.93
19p13.11	*HAPLN4*	Protein	-7.13	9.88×10^{-13}	0.02	rs2965183	172	0.22
19q13.31	***RP11-15A1.7*** [h]	lncRNA	5.45	5.06×10^{-8}	0.02	rs3760982	215	0.28

[#] not yet reported from eQTL and/or functional studies as target genes of GWAS-identified risk variants and not harbor GWAS or fine-mapping identified risk variants

[a] Genes that were siRNA-silenced for functional assays are bolded; SNPs used to predict gene expression are listed in the Supplementary Table 13

[b] Protein: protein coding genes; lncRNA: long non-coding RNAs
[c] *P* value: nominal *P* value from association analysis of 122,977 cases and 105,974 controls; the threshold after Bonferroni correction of 8,597 tests ($0.05/8{,}597=5.82\times10^{-6}$) was used; R^2: prediction performance (R^2) derived using GTEx data
[d] Risk SNPs identified in previous GWAS or fine-mapping studies. The risk SNP closest to the gene is presented. A full list of all risk SNPs, and their distances to the genes are presented in the **Supplementary Table 4**
[e] Use of COJO method[36]; all index SNPs in the corresponding region were adjusted in the conditional analyses
[f] Predicted expression of *RP11-73O6.3* and *L3MBTL3* was correlated (spearman R=0.88)
[g] Predicted expression of *AP006621.6* and *RPLP2* was correlated; predicted expression of *LRRC37A, KANSL1-AS1, and CRHR1* was correlated (spearman R>0.1)
[h] Predicted expression of *RP11-15A1.7* and *ZNF404* was correlated (spearman R=0.64)

Table 3. Eleven expression-trait associations for genes previously reported as potential target genes of GWAS-identified breast cancer risk variants or genes harboring risk variants

Region	Gene[a]	Type[b]	Z score	*P* value[c]	R^{2c}	Closest risk SNP[d]	Distance to the closest risk SNP (kb)	*P* value after adjusting for adjacent risk SNPs[e]	Association direction reported previously[f]	Reference
1p36.13	*KLHDC7A*	Protein	-5.67	1.40×10^{-8}	0.04	rs2992756	0.085	0.06	-	[7]
2q33.1	***ALS2CR12***	Protein	6.70	2.11×10^{-11}	0.10	rs1830298	intron of the gene	0.17	NA	[31]
2q33.1	*CASP8*	Protein	-8.05	8.51×10^{-16}	0.22	rs3769821	intron of the gene	0.16	-	[31,32]
5q14.1	*ATG10*	Protein	-6.65	2.85×10^{-11}	0.51	rs7707921	intron of the gene	0.21	NA	[9]
5q14.2	*ATP6AP1L*	Protein	-4.98	6.32×10^{-7}	0.63	rs7707921	37	0.98	NA	[9]
6q23.1	*L3MBTL3* [g]	Protein	-6.69	2.27×10^{-11}	0.10	rs6569648	208	0.44	NA	[6]
6q25.1	***RMND1***	Protein	4.76	1.95×10^{-6}	0.13	rs3757322	169	1.11×10^{-4}	mixed	[17]
11q13.1	*SNX32*	Protein	4.70	2.60×10^{-6}	0.19	rs3903072	18	0.17	NA	[33]
15q26.1	*RCCD1*	Protein	-7.18	7.23×10^{-13}	0.13	rs2290203	6	1.66×10^{-4}	-	[10]
17q22	***STXBP4***	Protein	6.69	2.21×10^{-11}	0.03	rs6504950	intron of the gene	0.90	+ in GTEx	[34,35]
19q13.31	***ZNF404*** [h]	Protein	7.42	1.15×10^{-13}	0.15	rs3760982	90	0.005	NA	[8]

[a] Genes that were siRNA silenced for functional assays are bolded; SNPs used to predict gene expression are listed in the Supplementary Table 13
[b] Protein: protein coding genes; lncRNA: long non-coding RNAs; NA: not available
[c] *P* value: nominal *P* value from association analysis of 122,977 cases and 105,974 controls; the threshold after Bonferroni correction of 8,597 tests ($0.05/8{,}597=5.82\times10^{-6}$) was used; R^2: prediction performance (R^2) derived using GTEx data .
[d] Risk SNPs identified in previous GWAS or fine-mapping studies. The risk SNP closest to the gene is presented. A full list of all risk SNPs, and their distances to the genes are presented in the **Supplementary Table 4**
[e] Use of COJO method[36]; all index SNPs in the corresponding region were adjusted for the conditional analyses
[f] -: inverse association; +: positive association; mixed: both inverse and positive associations reported; NA: not available
[g] Predicted expression of *L3MBTL3* and *RP11-73O6.3* was correlated (spearman R=0.88)
[h] Predicted expression of *ZNF404* and *RP11-15A1.7* was correlated (spearman R=0.64)

Table 4. Genes at GWAS-identified breast cancer risk loci (± 500kb of the index SNPs) whose predicted expression levels were associated with breast cancer risk at *p*-values between 5.82×10^{-6} and 1.05×10^{-3} (FDR corrected *p*-value≤0.05)

Region	Gene	Type[a]	Z score	*P* value[b]	R^{2}[b]	Closest risk SNP[c]	Distance to the closest risk SNP (kb)	*P* value after adjusting for adjacent risk SNPs[d]
1p34.1	*UQCRH*	Protein	-3.90	9.51×10^{-5}	0.12	rs1707302	168	0.06
1p22.3	*LMO4*	Protein	-3.76	1.73×10^{-4}	0.09	rs12118297	15	0.002
2p23.3	*DNAJC27-AS1*	lncRNA	3.84	1.24×10^{-4}	0.03	rs6725517	65	0.13
4p14	*KLHL5*	Protein	3.52	4.35×10^{-4}	0.13	rs6815814	230	0.03
5q11.2	*AC008391.1*	miRNA	-4.03	5.60×10^{-5}	0.13	rs16886113	242	0.76
6p22.1	*HCG14*	lncRNA	-3.47	5.19×10^{-4}	0.11	rs9257408	61	0.03
6p22.2	*TRNAI2*	miRNA	-3.71	2.09×10^{-4}	0.02	rs71557345	307	0.007
6q25.1	*MTHFD1L*	Protein	3.85	1.17×10^{-4}	0.10	rs3757318	491	2.36×10^{-4}
8q24.21	*PVT1*	transcript	3.85	1.20×10^{-4}	0.03	rs11780156	81	1.09×10^{-4}
9q33.3	*RP11-123K19.1*	lncRNA	-4.10	4.05×10^{-5}	0.05	rs10760444	20	1.26×10^{-4}
10q25.2	*RP11-57H14.3*	lncRNA	3.42	6.16×10^{-4}	0.08	rs7904519	108	0.002
10q26.13	*RP11-500G22.2*	lncRNA	4.48	7.54×10^{-6}	0.15	rs2981582	336	0.91
11p15.5	*PTDSS2*	Protein	-3.47	5.16×10^{-4}	0.04	rs6597981	312	0.02
11p15.5	*AP006621.5*	Protein	4.35	1.37×10^{-5}	0.51	rs6597981	19	0.01
11p15.5	*PIDD1*	Protein	4.24	2.28×10^{-5}	0.45	rs6597981	intron of the gene	0.12
11p15.5	*MRPL23-AS1*	lncRNA	-3.86	1.12×10^{-4}	0.10	rs3817198	95	0.06
11q13.1-11q13.2	*PACS1*	Protein	-3.59	3.36×10^{-4}	0.06	rs3903072	255	0.001
12p11.22	*RP11-860B13.1*	lncRNA	3.46	5.42×10^{-4}	0.17	rs10771399	221	0.86
13q22.1	*KLF5*	Protein	-4.08	4.44×10^{-5}	0.22	rs6562760	306	NA
14q24.1	*CTD-2566J3.1*	lncRNA	-3.84	1.22×10^{-4}	0.04	rs2588809	64	0.55
14q32.33	*C14orf79*	Protein	4.37	1.22×10^{-5}	0.11	rs10623258	240	0.91
15q26.1	*FES*	Protein	4.37	1.26×10^{-5}	0.21	rs2290203	73	3.04×10^{-6}
16q12.2	*BBS2*	Protein	3.97	7.23×10^{-5}	0.26	rs2432539	80	0.36
16q12.2	*CRNDE*	lncRNA	3.28	1.05×10^{-3}	0.02	rs28539243	271	0.69
16q24.2	*RP11-482M8.1*	lncRNA	3.32	9.16×10^{-4}	0.02	rs4496150	441	0.19

17q11.2	*GOSR1*	Protein	3.79	1.51×10^{-4}	0.10	rs146699004	376	0.04
17q21.2	*ATP6V0A1*	Protein	3.61	3.02×10^{-4}	0.03	rs72826962	162	0.01
17q21.2	*RP11-400F19.8*	transcript	-3.96	7.65×10^{-5}	0.01	rs72826962	122	6.62×10^{-4}
17q21.31	*RP11-105N13.4*	transcript	-4.51	6.46×10^{-6}	0.02	rs2532263	359	NA
17q25.3	*CBX8*	Protein	4.38	1.16×10^{-5}	0.05	rs745570	6	0.99
19p13.11	*CTD-2538G9.5*	lncRNA	3.56	3.76×10^{-4}	0.01	rs8170	432	4.38×10^{-4}
19p13.11	*HOMER3*	Protein	-3.87	1.08×10^{-4}	0.10	rs4808801	469	0.18
20q11.22	*CTD-3216D2.5*	lncRNA	4.03	5.60×10^{-5}	0.16	rs2284378	281	9.24×10^{-4}
22q13.1	*TRIOBP*	Protein	3.34	8.34×10^{-4}	0.07	rs738321	396	0.003
22q13.1	*RP5-1039K5.13*	lncRNA	3.73	1.93×10^{-4}	0.01	rs738321	99	0.053
22q13.1	*CBY1*	Protein	3.91	9.34×10^{-5}	0.05	chr22:39359355	289	0.06
22q13.1	*APOBEC3A*	Protein	-4.11	3.98×10^{-5}	0.07	chr22:39359355	0.2	0.02
22q13.2	*RP1-85F18.6*	lncRNA	3.52	4.28×10^{-4}	0.12	rs73161324	460	0.72

[a] Protein: protein coding genes; lncRNA: long non-coding RNAs; transcript: processed transcript

[b] *P* value: nominal *P* value from association analysis of 122,977 cases and 105,974 controls; R^2: prediction performance derived using GTEx data.

[c] Risk SNPs identified in previous GWAS or fine-mapping studies. The risk SNP closest to the gene is presented. A full list of all risk SNPs, and their distances to the genes are presented in the **Supplementary Table 4**

[d] Use of COJO method[36]; all index SNPs in the corresponding region were adjusted for the conditional analyses

Methods

The key elements of the study design, statistical parameters, materials and reagents, and human subjects are included in the **Life Sciences Reporting Summary**.

Building of gene expression prediction models

We used transcriptome and high-density genotyping data from the Genotype-Tissue Expression (GTEx) study to establish prediction models for genes expressed in normal breast tissues. Details of the GTEx have been described elsewhere[55]. Genomic DNA samples obtained from study subjects included in the GTEx were genotyped using Illumina OMNI 5M or 2.5M SNP Array and RNA samples from 51 tissue sites were sequenced to generate transcriptome profiling data. Genotype data were processed according to the GTEx protocol (see URLs). SNPs with a call rate < 98%, with differential missingness between the two array experiments (5M/2.5M Arrays), with Hardy-Weinberg equilibrium *p*-value < 10^{-6} (among subjects of European ancestry), or showing batch effects were excluded. One Klinefelter individual, three related individuals, and a chromosome 17 trisomy individual were also excluded. The genotype data were imputed to the Haplotype Reference Consortium reference panel[56] using Minimac3 for imputation and SHAPEIT for prephasing[57,58]. SNPs with high imputation quality ($r^2 \geq 0.8$), minor allele frequency (MAF) ≥ 0.05, and included in the HapMap Phase 2 version, were used to build expression prediction models. For gene expression data, we used Reads Per Kilobase per Million (RPKM) units from RNA-SeQC[59]. Genes with a median expression level of 0 RPKM across samples were removed, and the RPKM values of each gene were log2 transformed. We performed quantile normalization to bring the expression profile of each sample to the same scale, and performed inverse quantile normalization for each gene to map each set of expression

values to a standard normal. We adjusted for the top ten principal components (PCs) derived from genotype data and the top 15 probabilistic estimation of expression residuals (PEER) factors to correct for batch effects and experimental confounders in model building[60]. Genetic and transcriptome data from 67 female subjects of European descent without a prior breast cancer diagnosis were used to build gene expression prediction models for this study.

We built an expression prediction model for each gene by using the elastic net method as implemented in the glmnet R package, with $\alpha=0.5$, as recommended by Gamazon et al[27]. The genetically regulated expression for each gene was estimated by including variants within a 2 MB window flanking the respective gene boundaries, inclusive. Expression prediction models were built for protein coding genes, long non-coding RNAs (lncRNAs), microRNAs (miRNAs), processed transcripts, immunoglobulin genes, and T cell receptor genes, according to categories described in the Gencode V19 annotation file (see URLs). Pseudogenes were not included in the present study because of potential concerns of inaccurate calling[61]. Ten-fold cross-validation was used to validate the models internally. Prediction R^2 values (the square of the correlation between predicted and observed expression) were generated to estimate the prediction performance of each of the gene prediction models established.

For genes that cannot be predicted well using the above approach, we built models using only SNPs located in predicted promoter or enhancer regions in breast cell lines. This approach reduces the number of variants for model building, and thus potentially improves model accuracy, by increasing the ratio of sample size to effective degrees of freedom.

SNP-level annotation data in three breast cell lines, namely, Breast Myoepithelial Primary Cells (E027), Breast variant Human Mammary Epithelial Cells (vHMEC) (E028), and HMEC Mammary Epithelial Primary Cells (E119) in the Roadmap Epigenomics Project/Encyclopedia of DNA Elements Project[16], were downloaded from HaploReg (Version 4.0, assessed on December 6, 2016) (see URLs). SNPs in regions classified as promoters (TssA, TssAFlnk), enhancers (Enh, EnhG), or regions with both promoter and enhancer signatures (ExFlnk) according to the core 15 chromatin state model[16] in at least one of the cell lines were retained as input SNPs for model building.

Evaluating performance of gene expression prediction models using The Cancer Genome Atlas (TCGA) data

To assess further the validity of the models, we performed external validation using data generated in tumor-adjacent normal breast tissue samples obtained from 86 European-ancestry female breast cancer patients included in the TCGA. Genotype data were imputed using the same approach as described for GTEx data. Expression data were processed and normalized using a similar approach as described above. The predicted expression level for each gene was calculated using the model established using GTEx data and then compared with the observed level of that gene using the Spearman's correlation.

Evaluating statistical power for association tests

We conducted a simulation analysis to assess the power of our TWAS analysis. Specifically, we set the number of cases and controls to be 122,977 and 105,974, respectively, and generated the gene expression levels from the empirical distribution of predicted gene expression levels in the

BCAC. We calculated statistical power at $P<5.82\times10^{-6}$ (the significance level used in our TWAS) according to cis-heritability (h^2) which we aim to capture using gene expression prediction models (R^2). The results based on 1000 replicates are summarized in **Supplementary Figure 8**. Based on the power calculation, our TWAS analysis has 80% power to detect a minimum odds ratio of 1.11, 1.07, 1.05, 1.04, or 1.03 for breast cancer risk per one standard deviation increase (or decrease) in the expression level of a gene whose cis-heritability is 5%, 10%, 20%, 40%, or 60%, respectively.

Association analyses of predicted gene expression with breast cancer risk

We used the following criteria to select genes for the association analysis: 1) with a model prediction R^2 of ≥ 0.01 in GTEx and a Spearman's correlation coefficient of ≥ 0.1 in TCGA, 2) with a prediction R^2 of ≥ 0.09 in GTEx regardless of the performance in TCGA, 3) with a prediction R^2 of ≥ 0.01 in GTEx but unable to be evaluated in TCGA. The second group of genes was selected because some gene expression levels might have changed in TCGA tumor-adjacent normal tissues, and thus it is anticipated that some genes may show low prediction performance in TCGA data due to the influence of tumor growth[62,63]. Overall, a total of 8,597 genes met the criteria and were evaluated for their expression-trait associations.

To identify novel breast cancer susceptibility loci and genes, the MetaXcan method, as described elsewhere, was used for the association analyses[26]. Briefly, the formula:

$$Z_g \approx \sum_{l \in \text{Model}_g} w_{lg} \frac{\hat{\sigma}_l}{\hat{\sigma}_g} \frac{\hat{\beta}_l}{\text{se}(\hat{\beta}_l)}$$

was used to estimate the Z-score of the association between predicted expression and breast cancer risk. Here w_{lg} is the weight of SNP l for predicting the expression of gene g, $\hat{\beta}_l$and $\mathrm{se}(\hat{\beta}_l)$ are the GWAS association regression coefficient and its standard error for SNP l, and $\hat{\sigma}_l$ and $\hat{\sigma}_g$ are the estimated variances of SNP l and the predicted expression of gene g respectively. Therefore, the weights for predicting gene expression, GWAS summary statistics results, and correlations between model predicting SNPs are the input variables for the MetaXcan analyses. For this study we estimated correlations between SNPs included in the prediction models using the phase 3, 1000 Genomes Project data focusing on European population.

For the association analysis, we used the summary statistics data of genetic variants associated with breast cancer risk generated in 122,977 breast cancer patients and 105,974 controls of European ancestry from the Breast Cancer Association Consortium (BCAC). The details of the BCAC have been described elsewhere[7,9,13,64,65]. Briefly, 46,785 breast cancer cases and 42,892 controls of European ancestry were genotyped using a custom Illumina iSelect genotyping array (iCOGS) containing ~211,155 variants. A further 61,282 cases and 45,494 controls of European ancestry were genotyped using the OncoArray including 570,000 SNPs (see URLs). Also included in this analysis were data from nine GWAS studies including 14,910 breast cancer cases and 17,588 controls of European ancestry. Genotype data from iCOGS, OncoArray and GWAS were imputed using the October 2014 release of the 1000 Genomes Project data as reference. Genetic association results for breast cancer risk were combined using inverse variance fixed effect meta-analyses[7]. For our study, only SNPs with imputation $r^2 \geq 0.3$ were used. All participating BCAC studies were approved by their appropriate ethics review boards.

Relevant ethical regulations had been complied. This study was approved by the BCAC Data Access Coordination Committee.

Lambda 1,000 ($\lambda_{1,000}$) was calculated to represent a standardized estimate of the genomic inflation scaling to a study of 1,000 cases and 1,000 controls, using the following formula: $\lambda_{1,000}=1+(\lambda_{obs}-1) \times (1/n_{cases}+1/n_{controls})/(1/1{,}000_{cases}+1/1{,}000_{controls})$[66,67]. We used a Bonferroni corrected *p* threshold of 5.82×10^{-6} (0.05/8,597) to determine a statistically significant association for the primary analyses. To identify additional gene candidates at previously identified susceptibility loci, we also used a false discovery rate (FDR) corrected *p* threshold of 1.05×10^{-3} (FDR ≤ 0.05) to determine a significant association. Associated genes with an expression of >0.1 RPKM in less than 10 individuals in GTEx data were excluded as the corresponding prediction models may not be stable.

To determine whether the predicted expression-trait associations were independent of the top signals identified in previous GWAS, we performed GCTA-COJO analyses developed by Yang et al[36] to calculate association betas and standard errors of variants with breast cancer risk after adjusting for the index SNPs of interest. We then re-ran the MetaXcan analyses using the association statistics after conditioning on the index SNPs. This information was used to determine whether the detected expression-trait associations remained significant after adjusting for the index SNPs.

For 41 identified associated genes at the Bonferroni-corrected threshold, we also performed analyses using individual level data in iCOGS (n=84,740) and OncoArray (n=112,133) datasets.

We generated predicted gene expression using predicting SNPs (**Supplementary Table 12)**, and then assessed the association between predicted gene expression and breast cancer risk adjusting for study and nine principal components in iCOGS dataset, and country and the first ten principal components in OncoArray dataset. Conditional analyses adjusting for index SNPs were performed to assess potential influence of reported index SNPs on the association between predicted gene expression and breast cancer risk. Furthermore, we evaluated whether the predicted expression levels of genes within a same genomic region were correlated with each other by using the OncoArray data.

INQUISIT algorithm scores for TWAS-identified genes

To evaluate whether there are additional lines of evidence supporting the identified genes as putative target genes of GWAS identified risk SNPs beyond the scope of eQTL, we assessed their INQUISIT algorithm scores, which have been described elsewhere[7]. Briefly, this approach evaluates chromatin interactions between distal and proximal regulatory transcription-factor binding sites and the promoters at the risk regions using Hi-C data generated in HMECs[68] and Chromatin Interaction Analysis by Paired End Tag (ChiA-PET) in MCF7 cells. This could detect genome-wide interactions brought about by, or associated with, CCCTC-binding factor (CTCF), DNA polymerase II (POL2), and Estrogen Receptor (ER), all involved in transcriptional regulation[68]. Annotation of predicted target genes used the Integrated Method for Predicting Enhancer Targets (IM-PET)[69], the Predicting Specific Tissue Interactions of Genes and Enhancers (PreSTIGE) algorithm[70], Hnisz[71] and FANTOM[72]. Features contributing to the scores are based on functionally important genomic annotations such as chromatin interactions, transcription factor binding, and eQTLs. The detailed information for the INQUISIT pipeline and

scoring strategy has been included in a previous publication[7]. In brief, besides assigning integral points according to different features, we also set up-weighting and down-weighting criteria according to breast cancer driver genes, topologically associated domain (TAD) boundaries, and gene expression levels in relevant breast cell lines. Scores in the distal regulation category range from 0-7, and in the promoter category from 0-4. A score of "none" represents that no evidence was found for regulation of the corresponding gene.

Functional enrichment analysis using Ingenuity Pathway Analysis (IPA)

We performed functional enrichment analysis for the identified protein-coding genes reaching Bonferroni corrected association threshold. To assess potential functionality of the identified lncRNAs, we examined their co-expressed protein-coding genes determined using expression data of normal breast tissue of European females in GTEx. Spearman's correlations between protein-coding genes and identified lncRNAs of ≥ 0.4 or ≤ -0.4 were used to indicate a high co-expression. Canonical pathways, top associated diseases and biofunctions, and top networks associated with genes of interest were estimated using IPA software[37].

Gene expression in breast cell lines

Total RNA was isolated from 18 cell lines (**Supplementary Table 8**) using the RNeasy Mini Kit (Qiagen). cDNA was synthesized using the SuperScript III (Invitrogen) and amplified using the Platinum SYBR Green qPCR SuperMix-UDG cocktail (Invitrogen). Two or three primer pairs were used for each gene and the mRNA levels for each sample was measured in technical triplicates for each primer set. The primer sequences are listed in **Supplementary Table 13**. Experiments were performed using an ABI ViiA(TM) 7 System (Applied Biosystems), and data

processing was performed using ABI QuantStudio™ Software V1.1 (Applied Biosystems). The average of Ct from all the primer pairs for each gene was used to calculate ΔC_T. The relative quantitation of each mRNA normalizing to that in 184A1 was performed using the comparative Ct method ($\Delta\Delta C_T$) and summarized in **Supplementary Figure 4**.

Short interfering RNA (siRNA) silencing

184A1, MCF7 and T47D cells were reverse-transfected with siRNAs targeting genes of interest (GOI) or a non-targeting control siRNA (consi; Shanghai Genepharma) with RNAiMAX (Invitrogen) according to the manufacturer's protocol. Verification of siRNA knockdown of gene expression by qPCR was performed 36 hours after transfection.

Proliferation and colony formation assays

For proliferation assays, MCF7 and T47D cells were trypsinized at 16 hours post-transfection and seeded into 24 well plates to achieve ~10% confluency. Phase-contrast images were collected with IncuCyte ZOOM (Essen Bioscience) for seven days. Duplicate samples were assessed for each GOI siRNA transfected cells along with non-target control si (NTCsi) treated cells in the same plate. 184A1 cells were reverse-transfected in 96 well plates to achieve 50% confluence at 8 hours after transfection. Two independent experiments were carried out for all siRNAs in all three cell lines. Each cell proliferation time-course was normalized to the baseline confluency and analyzed in GraphPad Prism. The area under the curve was calculated for each concentration (n=4) and used to calculate corrected proliferation (Corrected proliferation % = 100 +/- (relative proliferation in indicated siRNA - proliferation in NTC siRNA) / knockdown efficiency ("+" if the GOI promotes proliferation and "-" if it inhibits proliferation)). For each

gene, results from two siRNAs in two independent experiments were averaged and summarized in **Figure 2** and **Supplementary Figure 6**. For colony formation assays; the same number of GOI siRNA transfected MCF7 cells was seeded in 6 well plates at 16 hours after transfection to assay colony forming efficiency at two weeks. All siRNA-treated cells were seeded in duplicate. Colonies (defined to consist of at least 50 cells) were fixed with methanol, stained with crystal violet (0.5% w/v), scanned and counted using ImageJ as batch analysis by a self-defined plug-in Macro. Correct CFE % = 100 +/- (relative CFE in indicated siRNA - CFE in NTC siRNA) / knockdown efficiency ("+" if the GOI promotes CF and "-" if it inhibits CF). For each gene, results from two siRNAs in two independent experiments were averaged and summarized in **Figure 2** and **Supplementary Figure 7**. *P*-values were determined by one-way ANOVA followed by Dunnett's multiple comparisons test.

Data availability

The GTEx data are publicly available via dbGaP (www.ncbi.nlm.nih.gov/gap; dbGaP Study Accession: phs000424.v6.p1). TCGA data are publicly available via National Cancer Institute's Genomic Data Commons Data Portal (https://gdc.cancer.gov/). A subset of the BCAC data that support the findings of this study is publically available via dbGaP (www.ncbi.nlm.nih.gov/gap; accession number phs001265.v1.p1). Most of the BCAC data used in this study are or will be publicly available via dbGAP. Data from some BCAC studies are not publicly available due to restraints imposed by the ethics committees of individual studies; requests for further data can be made to the BCAC (http://bcac.ccge.medschl.cam.ac.uk/) Data Access Coordination Committee (DACC). BCAC DACC approval is required to access data from studies ABCFS, ABCS, ABCTB, BBCC, BBCS, BCEES, BCFR-NY, BCFR-PA, BCFR-UT, BCINIS, BSUCH, CBCS,

CECILE, CGPS, CTS, DIETCOMPLYF, ESTHER, GC-HBOC, GENICA, GEPARSIXTO, GESBC, HABCS, HCSC, HEBCS, HMBCS, HUBCS, KARBAC, KBCP, LMBC, MABCS, MARIE, MBCSG, MCBCS, MISS, MMHS, MTLGEBCS, NC-BCFR, OFBCR, ORIGO, pKARMA, POSH, PREFACE, RBCS, SKKDKFZS, SUCCESSB, SUCCESSC, SZBCS, TNBCC, UCIBCS, UKBGS and UKOPS.

Code availability

The computer codes used in our study are available upon reasonable request.

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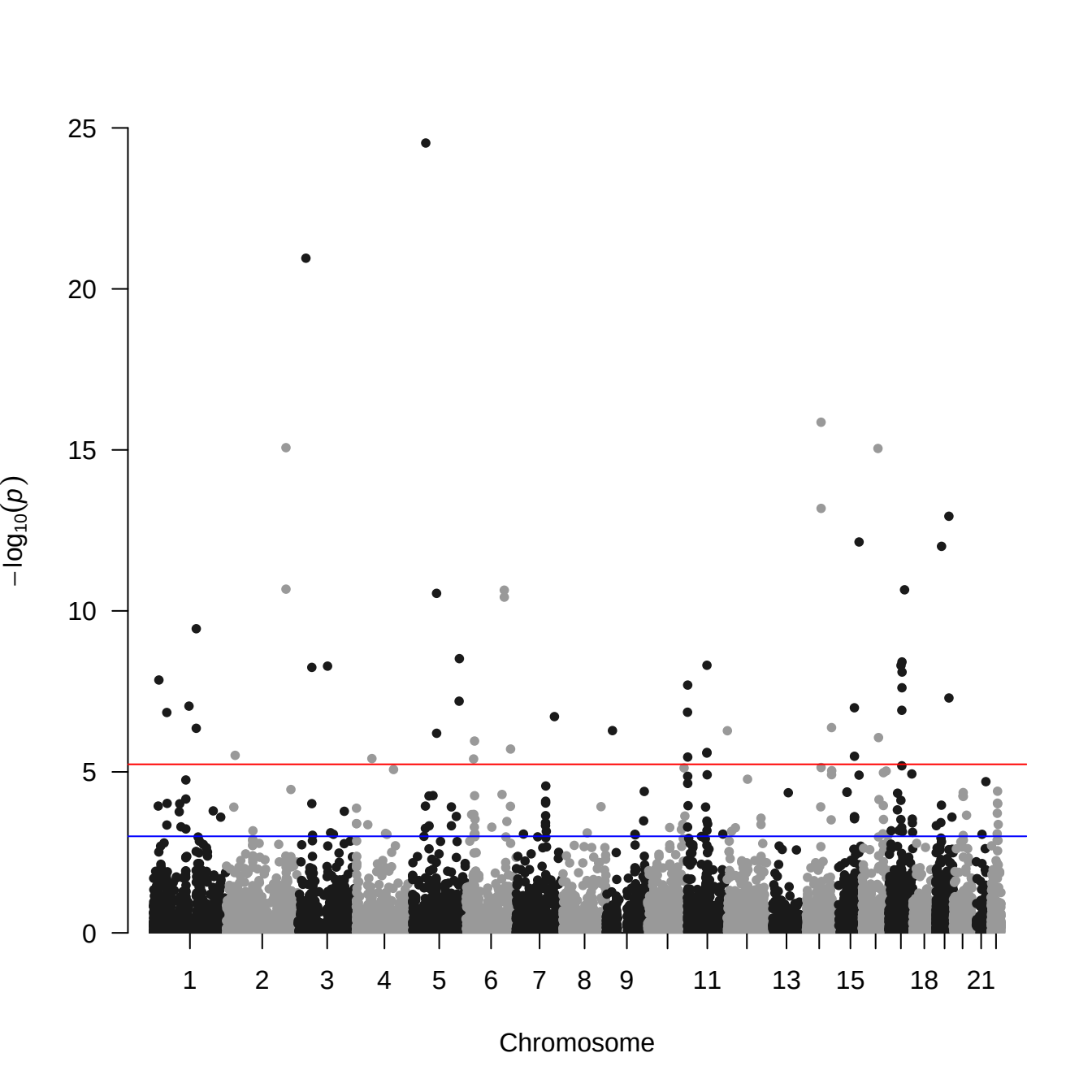
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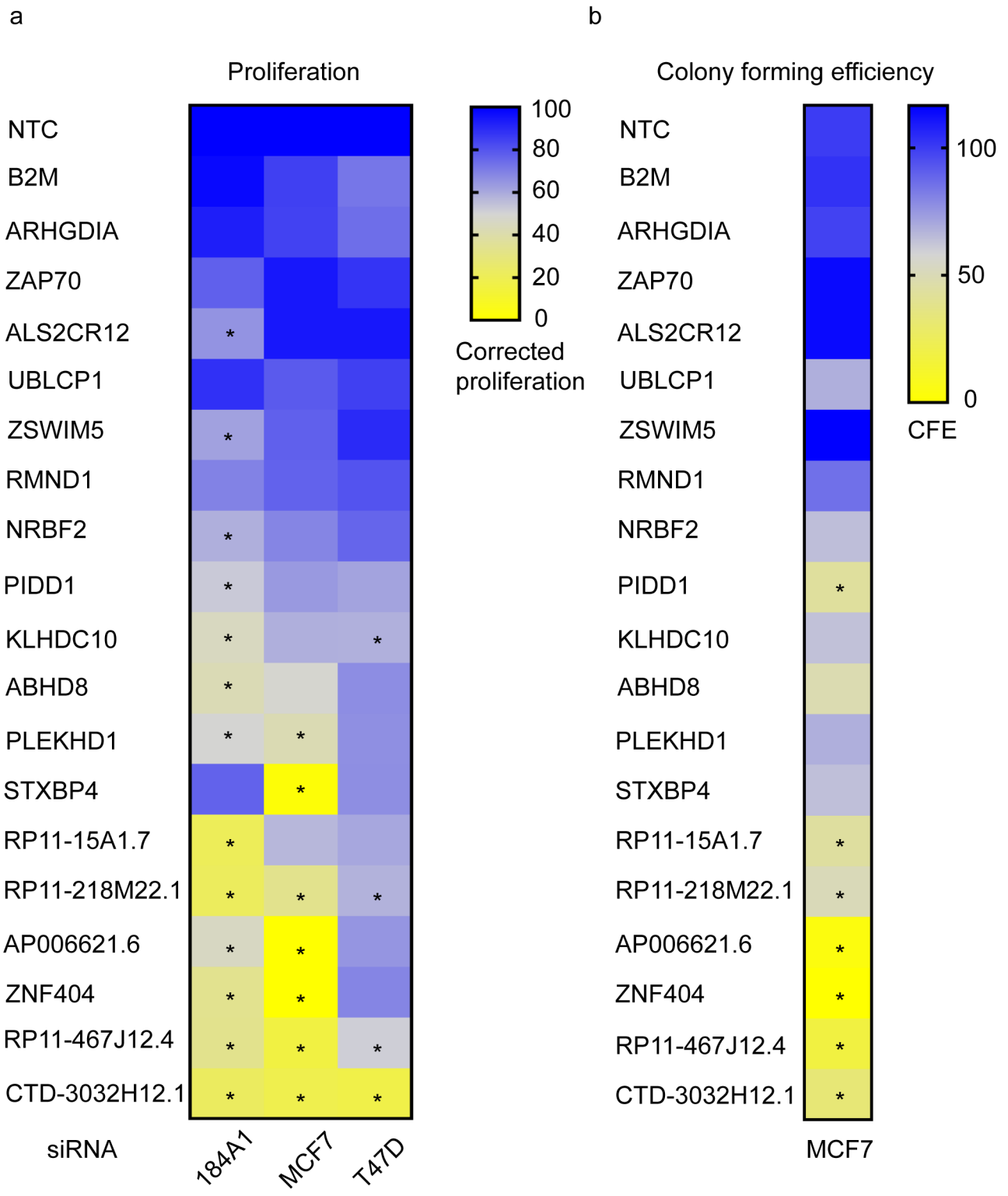
a
Proliferation
NTC
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ALS2CR12
UBLCP1
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RMND1
NRBF2
PIDD1
KLHDC10
ABHD8
PLEKHD1
STXBP4
RP11-15A1.7
RP11-218M22.1
AP006621.6
ZNF404
RP11-467J12.4
CTD-3032H12.1
siRNA
184A1
MCF7
T47D
100
80
60
40
20
0
Corrected proliferation
b
Colony forming efficiency
NTC
B2M
ARHGDIA
ZAP70
ALS2CR12
UBLCP1
ZSWIM5
RMND1
NRBF2
PIDD1
KLHDC10
ABHD8
PLEKHD1
STXBP4
RP11-15A1.7
RP11-218M22.1
AP006621.6
ZNF404
RP11-467J12.4
CTD-3032H12.1
MCF7
100
50
0
CFE

Gene	Type*	Z score	*P* value	R^2
RP11-53O19.1	lncRNA	10.38	2.94×10^{-25}	0.03
LRRC3B	Protein	-9.57	1.11×10^{-21}	0.17
GALNT16	Protein	-8.27	1.38×10^{-16}	0.04
CASP8	Protein	-8.05	8.51×10^{-16}	0.22
RP11-467J12.4	lncRNA	8.04	9.02×10^{-16}	0.23
PLEKHD1	Protein	7.5	6.55×10^{-14}	0.02
ZNF404	Protein	7.42	1.15×10^{-13}	0.15
RCCD1	Protein	-7.18	7.23×10^{-13}	0.13
HAPLN4	Protein	-7.13	9.88×10^{-13}	0.02
ALS2CR12	Protein	6.7	2.11×10^{-11}	0.1
STXBP4	Protein	6.69	2.21×10^{-11}	0.03
L3MBTL3	Protein	-6.69	2.27×10^{-11}	0.1
ATG10	Protein	-6.65	2.85×10^{-11}	0.51
RP11-73O6.3	lncRNA	-6.61	3.74×10^{-11}	0.11
NUDT17	Protein	-6.27	3.58×10^{-10}	0.01
UBLCP1	Protein	5.93	3.04×10^{-9}	0.07
LRRC37A	Protein	-5.89	3.85×10^{-9}	0.43
B3GNT1	Protein	-5.85	4.88×10^{-9}	0.09
LINC00671	lncRNA	-5.85	4.95×10^{-9}	0.07
RP11-114I8.4	lncRNA	-5.84	5.19×10^{-9}	0.02
PRSS46	Protein	-5.83	5.68×10^{-9}	0.13
LRRC37A2	Protein	-5.77	7.93×10^{-9}	0.46
KLHDC7A	Protein	-5.67	1.40×10^{-8}	0.04
AP006621.6	lncRNA	5.61	2.01×10^{-8}	0.34
KANSL1-AS1	lncRNA	-5.58	2.44×10^{-8}	0.62
RP11-15A1.7	lncRNA	5.45	5.06×10^{-8}	0.02
RP11-32D16.1	lncRNA	-5.41	6.37×10^{-8}	0.09
RP11-439A17.7	lncRNA	-5.34	9.07×10^{-8}	0.22
MAN2C1	Protein	-5.32	1.02×10^{-7}	0.39
CRHR1	Protein	-5.29	1.22×10^{-7}	0.22
RIC8A	Protein	-5.27	1.40×10^{-7}	0.15
ZSWIM5	Protein	5.26	1.43×10^{-7}	0.17
KLHDC10	Protein	5.21	1.92×10^{-7}	0.14

CTD-3051D23.1	lncRNA	-5.06	4.21×10^{-7}	0.05
ANKRD34A	Protein	-5.05	4.42×10^{-7}	0.01
MIR31HG	lncRNA	-5.02	5.22×10^{-7}	0.12
RP11-218M22.1	lncRNA	5.02	5.27×10^{-7}	0.19
ATP6AP1L	Protein	-4.98	6.32×10^{-7}	0.63
CTD-3032H12.1	lncRNA	4.92	8.58×10^{-7}	0.03
UBD	Protein	-4.87	1.10×10^{-6}	0.13
RMND1	Protein	4.76	1.95×10^{-6}	0.13
RP11-867G23.10	transcript	4.71	2.49×10^{-6}	0.03
SNX32	Protein	4.7	2.60×10^{-6}	0.19
ALK	Protein	4.67	3.06×10^{-6}	0.06
CTD-2323K18.1	transcript	-4.65	3.27×10^{-6}	0.07
RPLP2	Protein	4.64	3.46×10^{-6}	0.27
SPATA18	Protein	-4.62	3.86×10^{-6}	0.11
BTN3A2	Protein	4.61	3.97×10^{-6}	0.28
RP11-105N13.4	transcript	-4.51	6.46×10^{-6}	0.02
SLC39A9	Protein	-4.48	7.32×10^{-6}	0.03
RP11-500G22.2	lncRNA	4.48	7.54×10^{-6}	0.15
FAT4	Protein	4.45	8.44×10^{-6}	0.06
CRIP2	Protein	4.44	9.14×10^{-6}	0.03
RP11-432I5.1	lncRNA	4.4	1.06×10^{-5}	0.03
CBX8	Protein	4.38	1.16×10^{-5}	0.05
C14orf79	Protein	4.37	1.22×10^{-5}	0.11
RHOD	Protein	4.37	1.23×10^{-5}	0.03
FES	Protein	4.37	1.26×10^{-5}	0.21
AP006621.5	Protein	4.35	1.37×10^{-5}	0.51
NUP107	Protein	4.3	1.69×10^{-5}	0.14
GSTM4	Protein	-4.29	1.78×10^{-5}	0.06
YBEY	Protein	4.26	2.01×10^{-5}	0.4
PIDD1	Protein	4.24	2.28×10^{-5}	0.45
RP11-126L15.4	lncRNA	-4.19	2.74×10^{-5}	0.05
AC010136.2	lncRNA	-4.14	3.52×10^{-5}	0.21
APOBEC3A	Protein	-4.11	3.98×10^{-5}	0.07
RP11-123K19.1	lncRNA	-4.1	4.05×10^{-5}	0.05
GABPB1-AS1	transcript	4.1	4.21×10^{-5}	0.45
CTD-3110H11.1	lncRNA	4.09	4.31×10^{-5}	0.53

EDEM2	Protein	4.09	4.39×10^{-5}	0.03
KLF5	Protein	-4.08	4.44×10^{-5}	0.22
HSF2	Protein	-4.05	5.02×10^{-5}	0.04
SMN2	Protein	-4.04	5.44×10^{-5}	0.19
XXbac-BPG170G13.32	lncRNA	4.03	5.50×10^{-5}	0.14
AC008391.1	miRNA	-4.03	5.60×10^{-5}	0.13
CTD-3216D2.5	lncRNA	4.03	5.60×10^{-5}	0.16
CPNE1	Protein	-4.02	5.80×10^{-5}	0.33
GSTM3	Protein	-3.98	6.95×10^{-5}	0.18
BBS2	Protein	3.97	7.23×10^{-5}	0.26
RP11-400F19.8	transcript	-3.96	7.65×10^{-5}	0.01
PILRA	Protein	3.94	8.16×10^{-5}	0.54
STAG3L5P-PVRIG2P-PILRB	transcript	3.91	9.27×10^{-5}	0.32
CBY1	Protein	3.91	9.34×10^{-5}	0.05
UQCRH	Protein	-3.9	9.51×10^{-5}	0.12
ALS2CL	Protein	-3.9	9.69×10^{-5}	0.23
ATF4	Protein	-3.9	9.74×10^{-5}	0.11
CCBL2	Protein	3.9	9.78×10^{-5}	0.01
HOMER3	Protein	-3.87	1.08×10^{-4}	0.1
CMTR2	Protein	-3.86	1.11×10^{-4}	0.01
MRPL23-AS1	lncRNA	-3.86	1.12×10^{-4}	0.1
ARHGEF19	Protein	-3.86	1.15×10^{-4}	0.13
NNT-AS1	lncRNA	3.86	1.15×10^{-4}	0.06
MTHFD1L	Protein	3.85	1.17×10^{-4}	0.1
PVT1	transcript	3.85	1.20×10^{-4}	0.03
CTD-2566J3.1	lncRNA	-3.84	1.22×10^{-4}	0.04
PDLIM4	Protein	-3.84	1.22×10^{-4}	0.08
MYRF	Protein	3.84	1.24×10^{-4}	0.01
DNAJC27-AS1	lncRNA	3.84	1.24×10^{-4}	0.03
ATP5I	Protein	-3.82	1.34×10^{-4}	0.02
GOSR1	Protein	3.79	1.51×10^{-4}	0.1
RP11-335O13.7	lncRNA	-3.77	1.63×10^{-4}	0.08
RP11-550I24.2	transcript	-3.76	1.67×10^{-4}	0.05
LMO4	Protein	-3.76	1.73×10^{-4}	0.09

RP5-1039K5.13	lncRNA	3.73	1.93×10^{-4}	0.01
TRNAI2	miRNA	-3.71	2.09×10^{-4}	0.02
RP4-625H18.2	lncRNA	-3.7	2.12×10^{-4}	0.02
ZNF334	Protein	-3.69	2.22×10^{-4}	0.12
PILRB	Protein	3.68	2.29×10^{-4}	0.3
METTL10	Protein	-3.68	2.35×10^{-4}	0.17
SH3TC2	Protein	3.67	2.42×10^{-4}	0.09
CTD-2026K11.3	lncRNA	3.67	2.46×10^{-4}	0.01
CTD-2026K11.2	lncRNA	3.66	2.52×10^{-4}	0.12
TMC4	Protein	3.66	2.54×10^{-4}	0.21
RP5-1139B12.4	lncRNA	-3.66	2.55×10^{-4}	0.17
TBX5	Protein	3.64	2.73×10^{-4}	0.11
SNUPN	Protein	-3.63	2.86×10^{-4}	0.03
RP11-1055B8.4	lncRNA	3.62	2.92×10^{-4}	0.2
PSORS1C2	Protein	3.62	2.96×10^{-4}	0.41
IST1	Protein	3.62	3.00×10^{-4}	0.01
ATP6V0A1	Protein	3.61	3.02×10^{-4}	0.03
KLC1	Protein	-3.61	3.08×10^{-4}	0.07
GPR144	Protein	3.59	3.31×10^{-4}	0.12
PACS1	Protein	-3.59	3.36×10^{-4}	0.06
ECT2L	Protein	3.58	3.47×10^{-4}	0.14
CTD-2538G9.5	lncRNA	3.56	3.76×10^{-4}	0.01
AZGP1	Protein	-3.55	3.79×10^{-4}	0.03
OXLD1	Protein	3.55	3.86×10^{-4}	0.15
CPLX1	Protein	-3.54	4.03×10^{-4}	0.05
DGKQ	Protein	3.54	4.06×10^{-4}	0.25
RP11-757G1.6	lncRNA	3.53	4.17×10^{-4}	0.19
CTA-109P11.4	lncRNA	-3.52	4.26×10^{-4}	0.1
RP1-85F18.6	lncRNA	3.52	4.28×10^{-4}	0.12
TBX5-AS1	lncRNA	3.52	4.31×10^{-4}	0.09
KLHL5	Protein	3.52	4.35×10^{-4}	0.13
MUTYH	Protein	3.51	4.47×10^{-4}	0.04
TRIM4	Protein	-3.5	4.64×10^{-4}	0.43
MIR1909	miRNA	3.5	4.68×10^{-4}	0.04
SLC22A5	Protein	-3.5	4.72×10^{-4}	0.19
CCDC18	Protein	-3.48	5.08×10^{-4}	0.38

PTDSS2	Protein	-3.47	5.16×10^{-4}	0.04
HCG14	lncRNA	-3.47	5.19×10^{-4}	0.11
SMIM8	Protein	3.47	5.20×10^{-4}	0.06
MAP3K14-AS1	lncRNA	-3.46	5.31×10^{-4}	0.04
FAM149B1	Protein	-3.46	5.35×10^{-4}	0.03
RP11-860B13.1	lncRNA	3.46	5.42×10^{-4}	0.17
PAIP1	Protein	-3.45	5.67×10^{-4}	0.02
GSTM5	Protein	-3.44	5.92×10^{-4}	0.28
RP11-57H14.3	lncRNA	3.42	6.16×10^{-4}	0.08
BRMS1	Protein	-3.4	6.62×10^{-4}	0.05
KDM6B	Protein	-3.4	6.73×10^{-4}	0.07
IGKV2D-24	IG_gene	-3.4	6.74×10^{-4}	0.02
RP11-174G6.5	lncRNA	3.39	7.00×10^{-4}	0.05
POLR2J	Protein	-3.39	7.01×10^{-4}	0.28
RP11-580I16.2	lncRNA	3.38	7.17×10^{-4}	0.04
RP13-20L14.1	lncRNA	-3.37	7.52×10^{-4}	0.02
RP11-553A10.1	Protein	3.36	7.76×10^{-4}	0.03
RP11-363E6.3	lncRNA	-3.36	7.83×10^{-4}	0.05
TSPAN5	Protein	-3.35	8.11×10^{-4}	0.04
PSORS1C1	Protein	3.34	8.28×10^{-4}	0.35
TRIOBP	Protein	3.34	8.34×10^{-4}	0.07
CLEC18A	Protein	-3.34	8.37×10^{-4}	0.43
DFNA5	Protein	-3.33	8.55×10^{-4}	0.19
TMEM136	Protein	3.33	8.56×10^{-4}	0.07
C9orf3	Protein	3.33	8.64×10^{-4}	0.03
GPR156	Protein	3.33	8.67×10^{-4}	0.19
IL10RB-AS1	lncRNA	-3.33	8.68×10^{-4}	0.17
BDH2	Protein	-3.33	8.72×10^{-4}	0.23
ZNF165	Protein	3.33	8.76×10^{-4}	0.06
LINC00092	lncRNA	-3.32	9.03×10^{-4}	0.08
RP11-482M8.1	lncRNA	3.32	9.16×10^{-4}	0.02
USP19	Protein	-3.31	9.28×10^{-4}	0.02
MMP24	Protein	-3.31	9.40×10^{-4}	0.13
CTD-2196P11.2	lncRNA	3.29	1.01×10^{-3}	0.04
NR1H3	Protein	3.29	1.01×10^{-3}	0.17
FLOT1	Protein	-3.28	1.03×10^{-3}	0.1

BAZ1B	Protein	-3.28	1.04×10^{-3}	0.14
AHI1	Protein	3.28	1.05×10^{-3}	0.23
CRNDE	lncRNA	3.28	1.05×10^{-3}	0.02
AL450992.2	lncRNA	-3.28	1.05×10^{-3}	0.03

* Protein: protein coding genes; lncRNA: long non-coding RNAs; miRNA: microRNA; trans

P value: nominal *p* value from association analysis of 122,977 cases and 105,974 controls; l
MetaXcan was used for the association analyses

No. of predicting variants used	No. of predicting variants in model	Proportion of predicting variants used (%)
8	15	53
46	46	100
53	53	100
15	15	100
142	142	100
6	6	100
32	32	100
22	22	100
53	53	100
4	4	100
58	60	97
5	5	100
57	61	93
26	26	100
7	7	100
2	3	67
31	32	97
26	27	96
1	1	100
14	14	100
45	46	98
120	121	99
15	15	100
41	41	100
70	72	97
2	2	100
44	46	96
93	94	99
27	27	100
31	31	100
15	15	100
67	67	100
52	53	98

25	26	96
1	1	100
1	1	100
47	48	98
64	67	96
23	23	100
31	31	100
91	91	100
5	5	100
17	17	100
47	48	98
23	23	100
45	45	100
43	43	100
66	66	100
15	16	94
24	24	100
8	8	100
42	54	78
12	12	100
11	14	79
12	12	100
5	5	100
24	24	100
23	23	100
46	46	100
4	4	100
9	9	100
27	27	100
61	61	100
59	59	100
1	1	100
33	33	100
21	21	100
28	28	100
25	26	96

58	59	98
30	30	100
45	45	100
33	34	97
50	56	89
7	7	100
57	57	100
36	36	100
23	23	100
20	20	100
22	26	85
25	25	100
42	43	98
19	21	90
35	35	100
1	3	33
95	97	98
13	17	76
16	16	100
22	38	58
13	14	93
95	96	99
40	40	100
24	24	100
14	17	82
16	16	100
42	43	98
10	10	100
22	22	100
9	9	100
13	13	100
34	34	100
61	61	100
1	1	100

37	38	97
12	12	100
5	5	100
55	55	100
70	71	99
25	25	100
42	43	98
20	20	100
109	130	84
6	6	100
47	47	100
85	85	100
4	4	100
5	5	100
29	32	91
18	18	100
98	99	99
37	37	100
53	75	71
49	49	100
3	3	100
7	7	100
5	5	100
31	31	100
17	17	100
85	85	100
33	33	100
10	10	100
88	88	100
55	61	90
106	109	97
12	12	100
72	74	97
33	34	97
28	28	100
94	94	100

31	31	100
2	2	100
20	20	100
3	3	100
12	12	100
14	14	100
2	2	100
20	20	100
2	2	100
7	7	100
36	52	69
1	1	100
26	27	96
86	86	100
4	4	100
8	9	89
31	33	94
37	37	100
12	12	100
17	20	85
22	23	96
32	32	100
28	28	100
68	78	87
23	26	88
69	71	97
91	92	99
41	41	100
17	17	100
43	43	100
37	37	100
5	6	83
2	2	100
28	29	97
52	53	98
60	63	95

63	63	100
13	14	93
22	25	88
6	6	100

script: processed transcript; IG_gene: immunoglobulin genes.

R^2: prediction performance (R^2) derived using GTEx data.

Gene name	OncoArray z-score	OncoArray *p*- value	iCOGS z-score
Table 1			
ZSWIM5	2.98	0.003	4.32
LRRC3B	-7.48	7.19×10^{-14}	-4.89
SPATA18	-3.09	0.002	-2.59
UBD	-1.55	0.12	-4.07
KLHDC10	2.15	0.03	4.39
MIR31HG	-4.35	1.35×10^{-5}	-2.9
RIC8A	-3.28	0.001	-3.12
B3GNT1	-2.7	0.007	-5
RP11-867G23.10	2.78	0.005	3.13
RP11-218M22.1	3.84	1.22×10^{-4}	3.33
GALNT16	-4.45	8.74×10^{-6}	-6.17
PLEKHD1	5.21	1.85×10^{-7}	3.96
MAN2C1	-4.08	4.47×10^{-5}	-3.49
CTD-2323K18.1	-3.69	2.23×10^{-4}	-2.62
Table 2			
RP11-439A17.7	-4.35	1.37×10^{-5}	-3.39
NUDT17	-3.53	4.19×10^{-4}	-4.99
ANKRD34A	-4.27	1.97×10^{-5}	-2.54
ALK	3.84	1.23×10^{-4}	3.23
PRSS46	-4.33	1.51×10^{-5}	-3.51
RP11-114I8.4	-4.2	2.66×10^{-5}	-3.15
RP11-53O19.1	8.29	1.17×10^{-16}	5.75
UBLCP1	4.72	2.34×10^{-6}	3.12
RP11-32D16.1	-3.75	1.75×10^{-4}	-3.66
BTN3A2	3.16	0.002	2.74
RP11-73O6.3	-5.34	9.31×10^{-8}	-2.24
AP006621.6	3.58	3.40×10^{-4}	3.92
RPLP2	3.43	5.93×10^{-4}	2.77
CTD-3051D23.1	-2.6	0.009	-3.36
RP11-467J12.4	5.75	8.73×10^{-9}	5.41
CTD-3032H12.1	2.93	0.003	2.95
LRRC37A	-4.13	3.56×10^{-5}	-3.08
KANSL1-AS1	-3.83	1.28×10^{-4}	-3.17
CRHR1	-3.58	3.39×10^{-4}	-2.81

LINC00671	-4.4	1.11×10^{-5}	-4.15
LRRC37A2	-3.93	8.47×10^{-5}	-3.18
HAPLN4	-5.49	4.01×10^{-8}	-5.1
RP11-15A1.7	3.65	2.59×10^{-4}	4.26
Table 3			
KLHDC7A	-4.69	2.77×10^{-6}	-3.53
ALS2CR12	4.98	6.25×10^{-7}	2.8
CASP8	-5.97	2.42×10^{-9}	-3.63
ATG10	-3	0.003	-5.83
ATP6AP1L	-2.4	0.02	-4.24
L3MBTL3	-5.42	5.89×10^{-8}	-2.38
RMND1	3.14	0.002	2.76
SNX32	2.41	0.02	3.8
RCCD1	-5.58	2.36×10^{-8}	-4.08
STXBP4	4.77	1.85×10^{-6}	4.01
ZNF404	4.76	1.96×10^{-6}	5.28
Table 4			
UQCRH	-3.13	0.002	-2.14
LMO4	-2.42	0.02	-2.53
DNAJC27-AS1	3.41	6.47×10^{-4}	1.37
KLHL5	2.34	0.02	1.96
AC008391.1	-2.84	0.004	-3
HCG14	-2.65	0.008	-2.54
TRNAI2	-2.26	0.02	-2.46
MTHFD1L	2.26	0.02	2.81
PVT1	2.12	0.03	2.73
RP11-123K19.1	-3.8	1.42×10^{-4}	-1.49
RP11-57H14.3	3.54	3.98×10^{-4}	1.5
RP11-500G22.2	3.09	0.002	3.15
PTDSS2	-1.69	0.09	-2.98
AP006621.5	2.8	0.005	3.13
PIDD1	1.61	0.11	3.7
MRPL23-AS1	-2.29	0.02	-2.04
PACS1	-1.4	0.16	-3.53
RP11-860B13.1	2.86	0.004	2.15
KLF5	-2.16	0.03	-2.38
CTD-2566J3.1	-2.53	0.01	-2.65
C14orf79	3.6	3.17×10^{-4}	1.89
FES	3.48	4.95×10^{-4}	1.82

BBS2	2.65	0.008	3.08
CRNDE	2.82	0.005	0.5
RP11-482M8.1	2.54	0.01	1.82
GOSR1	2.87	0.004	1.61
ATP6V0A1	2.23	0.03	2.74
RP11-400F19.8	-4.18	2.91×10^{-5}	0.36
RP11-105N13.4	-2.92	0.004	-2.64
CBX8	1.82	0.07	3.61
CTD-2538G9.5	1.61	0.11	3.17
HOMER3	-1.67	0.09	-2.92
CTD-3216D2.5	1.4	0.16	3.1
TRIOBP	3.77	1.63×10^{-4}	0.55
RP5-1039K5.13	2.43	0.02	1.68
CBY1	2.13	0.03	2.6
APOBEC3A	-3.44	5.87×10^{-4}	-1.37
RP1-85F18.6	1.68	0.09	2.94

sample sizes (n): 61,282 cases and 45,494 controls for OncoArray; 46,785 cases and MetaXcan was used for the association analyses

iCOGS *p*- value	GWAS z-score	GWAS p-value	Cochran's Q
1.57×10^{-5}	1.39	0.17	0.32
1.02×10^{-6}	-3.61	3.11×10^{-4}	2.09
0.01	-2.33	0.02	0.21
4.67×10^{-5}	-3.46	5.48×10^{-4}	1.54
1.16×10^{-5}	2.87	0.004	0.92
0.004	-0.53	0.6	0.98
0.002	-2.71	0.007	0.17
5.83×10^{-7}	-2.38	0.02	0.82
0.002	2.18	0.03	0.04
8.82×10^{-4}	0.86	0.39	0.35
6.82×10^{-10}	-3.67	2.40×10^{-4}	0.38
7.43×10^{-5}	3.96	7.36×10^{-5}	0.9
4.88×10^{-4}	-0.86	0.39	0.43
0.009	-1.27	0.21	0.42
6.90×10^{-4}	-0.32	0.75	0.88
5.91×10^{-7}	-1.98	0.047	0.3
0.01	-1.13	0.26	0.94
0.001	-0.08	0.94	0.84
4.41×10^{-4}	-1.78	0.08	0.31
0.002	-2.74	0.006	0.48
8.85×10^{-9}	3.23	0.001	2.16
0.002	1.98	0.047	0.8
2.51×10^{-4}	-1.53	0.13	0.09
0.006	2.06	0.04	0.12
0.03	-4.32	1.53×10^{-5}	3.39
8.75×10^{-5}	1.98	0.048	0.01
0.006	1.57	0.12	0.19
7.85×10^{-4}	-3.34	8.30×10^{-4}	0.45
6.28×10^{-8}	1.93	0.054	0.38
0.003	2.6	0.009	0.15
0.002	-3.07	0.002	0.58
0.002	-2.61	0.009	0.27
0.005	-2.93	0.003	0.45

3.32×10^{-5}	-0.25	0.8	0.82
0.001	-2.96	0.003	0.39
3.46×10^{-7}	-0.31	0.75	1.28
2.00×10^{-5}	0.78	0.44	0.38

4.11×10^{-4}	-0.62	0.53	0.91
0.005	4.24	2.21×10^{-5}	2.09
2.78×10^{-4}	-4.66	3.20×10^{-6}	2.3
5.60×10^{-9}	-2.65	0.008	1.27
2.20×10^{-5}	-1.87	0.06	0.51
0.02	-4.13	3.65×10^{-5}	3.13
0.006	2.41	0.02	0.18
1.45×10^{-4}	1.78	0.08	0.27
4.56×10^{-5}	-2.21	0.03	0.81
6.05×10^{-5}	2.46	0.01	0.28
1.28×10^{-7}	2.28	0.02	0.06

0.03	-1.19	0.23	0.32
0.01	-1.42	0.16	0.002
0.17	1.77	0.08	1.12
0.05	1.59	0.11	0.09
0.003	-0.36	0.72	0.27
0.01	0.02	0.99	0.37
0.01	-1.67	0.09	0.02
0.005	1.58	0.11	0.02
0.006	1.82	0.07	0.06
0.14	-1.44	0.15	1.37
0.13	0.09	0.93	1.31
0.002	1.01	0.31	0.1
0.003	-1.33	0.18	0.25
0.002	1.26	0.21	0.03
2.16×10^{-4}	2.42	0.02	0.82
0.04	-2.89	0.004	0.48
4.19×10^{-4}	-1.09	0.27	0.81
0.03	0.66	0.51	0.26
0.017	-3.16	0.002	0.54
0.008	-1.19	0.24	0.02
0.06	2.03	0.04	0.86
0.07	2.34	0.02	0.9

0.002	0.53	0.59	0.21
0.61	2.76	0.006	1.9
0.07	1.37	0.17	0.18
0.11	2.22	0.03	0.62
0.006	0.94	0.34	0.06
0.72	-3.47	5.28×10^{-4}	5.84
0.008	-2.32	0.02	0.15
3.04×10^{-4}	2.44	0.01	0.6
0.002	1.48	0.14	0.39
0.004	-2.45	0.01	0.41
0.002	3.18	0.001	0.98
0.58	0.92	0.36	2.46
0.09	2.67	0.008	0.56
0.009	2.29	0.02	0.14
0.17	-2.6	0.009	1.4
0.003	1.48	0.14	0.24

d 42,892 controls for iCOGS; and 14,910 cases and 17,588 controls for GWA

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Gene	Risk SNP(s)[#]
Table 1	
ZSWIM5	rs1707302
LRRC3B	rs12493607 rs653465 rs4973768
SPATA18	rs6815814
UBD	rs9257408
KLHDC10	rs4593472
MIR31HG	rs1011970
RIC8A	rs6597981 rs3817198
B3GNT1	rs3903072
RP11-867G23.10	rs3903072
RP11-218M22.1	rs12422552
GALNT16	rs999737
PLEKHD1	rs999737
MAN2C1	rs2290203
CTD-2323K18.1	rs2290203
Table 2	
RP11-439A17.7	rs11249433
NUDT17	rs12405132
ANKRD34A	rs12405132
ALK	rs4577244
PRSS46	rs6796502
RP11-114I8.4	rs9833888
RP11-53O19.1	rs10941679 rs4415084
UBLCP1	rs1432679
RP11-32D16.1	rs1432679
BTN3A2	rs71557345
RP11-73O6.3	rs6569648
AP006621.6	rs6597981 rs909116 rs3817198
RPLP2	rs6597981 rs909116 rs3817198
CTD-3051D23.1	rs10623258
RP11-467J12.4	rs12922061 rs17817449 rs11075995 rs3112612 rs3803662 rs28539243
	rs12922061

CTD-3032H12.1	rs17817449 rs11075995 rs3112612 rs3803662 rs28539243
LINC00671	rs72826962
LRRC37A	rs2532263
KANSL1-AS1	rs2532263
CRHR1	rs2532263
LRRC37A2	rs2532263
HAPLN4	rs8170 rs2363956 rs4808801 rs2965183
RP11-15A1.7	rs3760982

Table 3

KLHDC7A	rs2992756
ALS2CR12	rs3769821 rs13393577 rs1830298
CASP8	rs3769821 rs13393577
ATG10	rs7707921
ATP6AP1L	rs7707921
L3MBTL3	rs6569648
RMND1	rs9383951 rs9485372 rs3757322 rs9397437 rs851984 rs9918437 rs2747652
SNX32	rs3903072 rs75915166 rs78540526
RCCD1	rs2290203
STXBP4	rs6504950 rs2787486
ZNF404	rs3760982

Table 4

UQCRH	rs1707302
LMO4	rs17426269 rs12118297
DNAJC27-AS1	rs6725517 rs200648189
KLHL5	rs6815814
	rs16886113

AC008391.1	rs16886181 rs16886397 rs2229882 rs7726354 rs62355902
HCG14	rs9257408
TRNAI2	rs71557345
MTHFD1L	rs3757318 rs2046210 rs9383938
PVT1	rs11780156 rs13281615 rs1562430
RP11-123K19.1	rs10760444
RP11-57H14.3	rs7904519
RP11-500G22.2	rs2981582 rs11199914 rs35054928 rs45631563
PTDSS2	rs6597981
AP006621.5	rs6597981
PIDD1	rs6597981
MRPL23-AS1	rs3817198
PACS1	rs3903072
RP11-860B13.1	rs10771399 rs7297051
KLF5	rs6562760
CTD-2566J3.1	rs2588809 rs999737
C14orf79	rs10623258
FES	rs2290203
BBS2	rs2432539
CRNDE	rs28539243
RP11-482M8.1	rs4496150
GOSR1	rs146699004
ATP6V0A1	rs72826962
RP11-400F19.8	rs72826962
RP11-105N13.4	rs2532263
CBX8	rs745570
CTD-2538G9.5	rs8170 rs2363956 rs67397200
HOMER3	rs4808801 rs2965183
CTD-3216D2.5	rs2284378
TRIOBP	rs738321

RP5-1039K5.13	rs738321
CBY1	rs738321 chr22:39359355
APOBEC3A	rs738321 chr22:39359355
RP1-85F18.6	rs73161324 rs6001930

[#] risk SNPs identified in previous GWAS or fine-mapping studies

Distance to the risk SNP (kb)
829
3931
591
705
14,101
597
892
502
588
1694
530
594
13,641
691
917
15,851
15,619
442
56
169
295
89
356
39
82
446
283
229
105
21
1160
1127
7
1129
1096
97
434-1595

290-2385
190
118
18
339
336
1977
1972
795
172
215
0.085
30
11075
inside the gene
inside the gene
11144
inside the gene
37
208
169-2117
18
3755
3707
6
inside the gene
inside the gene
90
168
342
15
65
455
230
242

276
381
416
504
301
61
307
491
525
564
81
451
419
20
108
336
594
347
339
312
19
inside the gene
95
255
221
241
306
64
438
240
73
80
271
441
376
162
122
359
6
432
437
444
469
494
281
396

99
484
289
780
0.2
460
689

Gene(s)	Top canonical pathways
Protein-coding genes with Bonferroni corrected significant associations	Granzyme B Signaling (p =0.024); Inflammasome pathway (p =0.030); Tumoricidal Function of Hepatic Natural Killer Cells (p =0.036); Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells (p =0.046)
MIR31HG	BER pathway (p =7.56×10^{-3}); Dermatan Sulfate Biosynthesis (Late Stages) (p =0.026); Chondroitin Sulfate Biosynthesis (Late Stages) (p =0.028); Ephrin A Signaling (p =0.030); Heparan Sulfate Biosynthesis (Late Stages) (p =0.030)
RP11-218M22.1	Netrin Signaling (p =0.024); ATM Signaling (p =0.037); Role of BRCA1 in DNA Damage Response (p =0.048)
CTD-2323K18.1	D-glucuronate Degradation I (p =3.31×10^{-3}); Methylglyoxal Degradation III (p =0.012); Mevalonate Pathway I (p =0.013);; Superpathway of Geranylgeranyldiphosphate Biosynthesis I (via Mevalonate) (p =0.018);; Tryptophan Degradation X (Mammalian, via Tryptamine) (p =0.020);
RP11-439A17.7	Tetrahydrobiopterin Biosynthesis I (p =2.21×10^{-3}); Tetrahydrobiopterin Biosynthesis II (p =2.21×10^{-3}); Relaxin Signaling (p =4.13×10^{-3}); Synaptic Long Term Depression (p =4.29×10^{-3}); Endothelin-1

	(p =4.38 × 10^{-3}); Endothelin-1 Signaling (p =6.60 × 10^{-3})
RP11-114I8.4	ErbB2-ErbB3 Signaling (p =0.043); ErbB4 Signaling (p =0.045)
RP11-53O19.1	Inosine-5'-phosphate Biosynthesis II (p =5.44 × 10^{-3}); Retinoate Biosynthesis II (p =7.25 × 10^{-3}); Purine Nucleotides De Novo Biosynthesis II (p =0.020); Cleavage and Polyadenylation of Pre-mRNA (p =0.022); Epithelial Adherens Junction Signaling (p =0.028)

RP11-32D16.1	AMPK Signaling ($p = 1.96 \times 10^{-4}$); Tyrosine Degradation I ($p = 2.20 \times 10^{-4}$); Phenylalanine Degradation IV (Mammalian, via Side Chain) ($p = 1.95 \times 10^{-3}$); LPS/IL-1 Mediated Inhibition of RXR Function ($p = 3.11 \times 10^{-3}$); Valine Degradation I ($p = 3.23 \times 10^{-3}$)
RP11-73O6.3	Pentose Phosphate Pathway (Oxidative Branch) ($p = 5.88 \times 10^{-3}$); Selenocysteine Biosynthesis II (Archaea and Eukaryotes) ($p = 8.81 \times 10^{-3}$); GDP-mannose Biosynthesis ($p = 8.81 \times 10^{-3}$); p53 Signaling ($p = 9.13 \times 10^{-3}$); Tryptophan Degradation to 2-amino-3-carboxymuconate Semialdehyde ($p = 0.010$)
AP006621.6	Primary Immunodeficiency Signaling ($p = 1.40 \times 10^{-3}$); Acetate Conversion to Acetyl-CoA ($p = 5.04 \times 10^{-3}$); T Cell Receptor Signaling ($p = 6.49 \times 10^{-3}$); G12/13 Signaling ($p = 9.50 \times 10^{-3}$); Tec Kinase Signaling ($p = 0.016$)

CTD-3051D23.1	Granulocyte Adhesion and Diapedesis (p =0.039); Agranulocyte Adhesion and Diapedesis (p =0.043); IL-22 Signaling (p =0.045); Role of JAK family kinases in IL-6-type Cytokine Signaling (p =0.046); B Cell Development (p =0.050)
RP11-467J12.4	Glycerol-3-phosphate Shuttle (p =2.32×10^{-3}); Glycerol Degradation I (p =5.78×10^{-3})
CTD-3032H12.1	ERK/MAPK Signaling (p =2.00×10^{-4}); FLT3 Signaling in Hematopoietic Progenitor Cells (p =1.14×10^{-3}); Acute Myeloid Leukemia Signaling (p =1.50×10^{-3}); -Adrenergic Signaling (p =1.92×10^{-3}); Corticotropin

	Releasing Hormone Signaling ($p = 3.69 \times 10^{-3}$)
KANSL1-AS1	Endoplasmic Reticulum Stress Pathway ($p = 0.024$); Tumoricidal Function of Hepatic Natural Killer Cells ($p = 0.027$); Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells ($p = 0.035$); TWEAK Signaling ($p = 0.038$)
LINC00671	Dolichyl-diphosphooligosaccharide Biosynthesis ($p = 0.016$); Hereditary Breast Cancer Signaling ($p = 0.017$); Antiproliferative Role of TOB in T Cell Signaling ($p = 0.037$); Inhibition of Angiogenesis by TSP1 ($p = 0.046$)
	Induction of Apoptosis by HIV1

RP11-15A1.7	($p = 1.09 \times 10^{-4}$); Docosahexaenoic Acid (DHA) Signaling ($p = 1.72 \times 10^{-3}$); Molecular Mechanisms of Cancer ($p = 2.33 \times 10^{-3}$); CD27 Signaling in Lymphocytes ($p = 2.93 \times 10^{-3}$); Small Cell Lung Cancer Signaling ($p = 5.60 \times 10^{-3}$)

NA: not available
p-values calculated using the right-tailed Fisher Exact Test

Related diseases and disorders	Molecular and Cellular Functions
Cancer; Developmental Disorder; Hematological Disease; Hereditary Disorder; Immunological Disease	Cell Death and Survival; Cell-To-Cell Signaling and Interaction; Cellular Compromise; Cell Cycle; Cellular Morphology
Cardiovascular Disease; Connective Tissue Disorders; Dermatological Diseases and Conditions; Developmental Disorder; Hereditary Disorder	Cell-To-Cell Signaling and Interaction; Cellular Assembly and Organization; Cellular Movement; Gene Expression; Molecular Transport
Cancer; Dermatological Diseases and Conditions; Developmental Disorder; Hereditary Disorder; Neurological Disease	Cell Cycle; DNA Replication, Recombination, and Repair; Cell Death and Survival; Cell Morphology; Cellular Assembly and Organization
Cancer; Cardiovascular Disease; Dermatological Diseases and Conditions; Endocrine System Disorders; Hereditary Disorder	DNA Replication, Recombination, and Repair; Post-Translational Modification; Carbohydrate Metabolism; Cell Morphology; Cellular Assembly and Organization
Developmental Disorder; Hereditary Disorder; Metabolic Disease; Neurological Disease; Ophthalmic Disease	Cell Signaling; DNA Replication, Recombination, and Repair; Nucleic Acid Metabolism; Small Molecule Biochemistry; Cell Morphology

Dermatological Diseases and Conditions; Developmental Disorder; Hereditary Disorder; Metabolic Disease; Organismal Injury and Abnormalities	Cellular Function and Maintenance; Molecular Transport; Cell Morphology; Gene Expression; Protein Trafficking
Dermatological Diseases and Conditions; Developmental Disorder; Hereditary Disorder; Neurological Disease; Ophthalmic Disease	Cell Cycle; Cell Morphology; Cellular Assembly and Organization; Cellular Function and Maintenance; Nucleic Acid Metabolism

Metabolic Disease; Endocrine System Disorders; Gastrointestinal Disease; Hepatic System Disease; Organismal Injury and Abnormalities	Lipid Metabolism; Small Molecule Biochemistry; Energy Production; Molecular Transport; Carbohydrate Metabolism
Cardiovascular Disease; Connective Tissue Disorders; Developmental Disorder; Hematological Disease; Hereditary Disorder	Cell Death and Survival; Carbohydrate Metabolism; Cell Cycle; Cell Morphology; Cell-To-Cell Signaling and Interaction
Cancer; Cardiovascular Disease; Connective Tissue Disorders; Dermatological Diseases and Conditions; Developmental Disorder	Cellular Function and Maintenance; Cell Death and Survival; Cell Morphology; Cell-To-Cell Signaling and Interaction; Cellular Development

Cancer; Cardiovascular Disease; Developmental Disorder; Endocrine System Disorders; Hematological Disease	Cellular Development; Cell Morphology; Cellular Growth and Proliferation; Lipid Metabolism; Molecular Transport
Cancer; Organismal Injury and Abnormalities; Reproductive System Disease; Cardiovascular Disease; Developmental Disorder	Cell-To-Cell Signaling and Interaction; Cellular Assembly and Organization; Cellular Growth and Proliferation; Cell Morphology; Cellular Development
Inflammatory Response; Cancer; Organismal Injury and Abnormalities; Auditory Disease; Cardiovascular Disease	Cell-To-Cell Signaling and Interaction; Cell Death and Survival; Cell Cycle; Cell Morphology; Cellular Function and Maintenance

Developmental Disorder; Hereditary Disorder; Neurological Disease; Organismal Injury and Abnormalities; Psychological Disorders	Cell Morphology; Cellular Function and Maintenance; Lipid Metabolism; Molecular Transport; Small Molecule Biochemistry
Inflammatory Response; Cancer; Cardiovascular Disease; Developmental Disorder; Gastrointestinal Disease	DNA Replication, Recombination, and Repair; Cell-To-Cell Signaling and Interaction; Cellular Function and Maintenance; Cell Cycle; Cellular Development

Infectious Diseases; Cancer; Cardiovascular Disease; Dermatological Diseases and Conditions; Developmental Disorder	Cellular Compromise; Cellular Assembly and Organization; Cell Morphology; Cell Death and Survival; Cell-To-Cell Signaling and Interaction

Top networks
Cell Death and Survival, Cellular Compromise, Nervous System Development and Function; Cancer, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities; Cardiovascular System Development and Function, Cell Cycle, Cellular Development; Cellular Assembly and Organization, DNA Replication, Recombination, and Repair, Cell Cycle; Developmental Disorder, Hereditary Disorder, Ophthalmic Disease
Cancer, Organismal Injury and Abnormalities, Reproductive System Disease; Cell Cycle, Connective Tissue Disorders, Dermatological Diseases and Conditions; Cardiovascular Disease, Cellular Development, Organismal Injury and Abnormalities; Cancer, Gastrointestinal Disease, Organismal Injury and Abnormalities; Hereditary Disorder,
Cell Cycle, Cellular Development, Cellular Growth and Proliferation; Cancer, Cell Death and Survival, Organismal Injury and Abnormalities; Developmental Disorder, Hereditary Disorder, Organismal Injury and Abnormalities
Cellular Assembly and Organization, Hereditary Disorder, Organismal Injury and Abnormalities; Cellular Development, Cellular Growth and Proliferation, Cell Death and Survival; Cell Morphology, Cellular Function and Maintenance, Hematological System Development and Function; Cell Cycle, Cell Morphology, Organ Morphology
Cell Morphology, Gastrointestinal Disease, Organismal Injury and Abnormalities; Cellular Development, Reproductive System Development and Function, Cell Cycle; Organ Morphology, Reproductive System Development and Function, Connective

Development and Function, Connective Tissue Disorders
Cell Morphology, Cellular Compromise, Cellular Function and Maintenance; Lipid Metabolism, Small Molecule Biochemistry, Dermatological Diseases and Conditions; Hereditary Disorder, Nephrosis, Ophthalmic Disease; Molecular Transport, Cellular Assembly and Organization, Cell Morphology; Cellular Assembly and Organization, Cellular Function and Maintenance, Cell Signaling
Cell Cycle, Cell-To-Cell Signaling and Interaction, Cellular Growth and Proliferation; Cell Death and Survival, Neurological Disease, Organismal Injury and Abnormalities; Cancer, Cell Death and Survival, Cell-To-Cell Signaling and Interaction; Cardiovascular Disease, Cell Death and Survival, Cell Morphology; Embryonic Development, Organismal Development, Tissue Morphology

Lipid Metabolism, Molecular Transport, Small Molecule Biochemistry; Cell Signaling, Nucleic Acid Metabolism, Small Molecule Biochemistry; Cell Cycle, Gene Expression, Organ Morphology; Carbohydrate Metabolism, Molecular Transport, Small Molecule Biochemistry; Skeletal and Muscular Disorders, Cell Morphology, Organ Development
Cellular Development, Cellular Growth and Proliferation, Reproductive System Development and Function; Cell-mediated Immune Response, Cellular Development, Cellular Function and Maintenance
Humoral Immune Response, Protein Synthesis, Hematological System Development and Function; Cellular Compromise, Cell Cycle, Cellular Assembly and Organization; Cell Cycle, Hereditary Disorder, Neurological Disease; Embryonic Development, Organismal Development, Tissue Development

Cell Cycle, Cell Death and Survival, Cellular Compromise; Cellular Development, Cellular Growth and Proliferation, Hematological System Development and Function; Cellular Assembly and Organization, Cellular Function and Maintenance, Tissue Morphology; Connective Tissue Disorders, Organismal Injury and Abnormalities, Reproductive System Development and Function; Infectious Diseases, Cancer, Organismal Injury and Abnormalities
Cardiovascular System Development and Function, Cellular Development, Cellular Function and Maintenance; Cell Morphology, Connective Tissue Development and Function, Tissue Morphology
Embryonic Development, Organ Development, Organismal Development; Cell Morphology, Cell Death and Survival, Cellular Development; Lipid Metabolism, Molecular Transport, Small Molecule Biochemistry; Post-Translational Modification, Cell Morphology, Cellular Function and Maintenance; Dermatological

Function and Maintenance, Dermatological Diseases and Conditions, Organismal Injury and Abnormalities, Hair and Skin Development and Function
Gene Expression, Cell Cycle, Lipid Metabolism; Cell Cycle, Reproductive System Development and Function, Embryonic Development; Developmental Disorder, Hereditary Disorder, Ophthalmic Disease; Cell Cycle, Endocrine System Development and Function, Lipid Metabolism
Cell Death and Survival, Cancer, Organismal Injury and Abnormalities; Cell Morphology, Developmental Disorder, Digestive System Development and Function; Cellular Movement, Nervous System Development and Function, Embryonic Development; Cell Morphology, Cellular Function and Maintenance, Cellular Movement; Organ Morphology, Organismal Development, Organismal Injury and Abnormalities

Cell Morphology, Cellular Assembly and Organization, Behavior; Cell Morphology, Cellular Function and Maintenance, Cellular Compromise; Cell Signaling, Nucleic Acid Metabolism, Molecular Transport; Cell Death and Survival, Cellular Development, Cellular Growth and Proliferation

List of highly co-expressed genes for each long non-coding RNA
NA
STMN4,ROCK1,APOL2,PRSS35,RPP38,RPUSD3,HS3ST6,LRR1,DIRC1,KLHL38,POLE,TREX2,CACNA1H,AC078883.4,RP5-826L7.1,MYLKP1,TSSK1A,MTHFD1P1,RP11-527F13.1,RP11-32B5.1,PRKCQ-AS1,RP11-834C11.3,CTD-2127H9.1,RP11-454K7.1,CTD-2561B21.10
FFAR2,PKIB,TP53BP2,LSM14B,NSA2,SYAP1,ZNF738,MAGEF1,FOXI2,DCC,NCR1,XRCC2,BLM,RP11-94I2.1,LINC00160,AC092664.1,RP11-83M16.2,CTD-2325P2.4,CTD-3099C6.7
VCAN,UBE2T,SUV39H1,MVK,AKR1A1,ZC3H13,MCM8,CASD1,CBLN2,DTL,DGKQ,RPL7A,CCDC74B,CTRC,RHEBL1,SNUPN,PKIA,KIF24,BMPR2,MUC19,LINC00612,RP11-157J24.1,LINC00035,RP11-460N20.4,FTH1P1,HNRNPA1P27,FAM203A,RP5-903G2.2,RP11-532F12.5,RP11-340F14.5,RP11-120M18.2,RP11-168F9.2
TBC1D23,SPR,GNA13,TRMT5,BAIAP2L2,GATA5,GUCY2D,NIPA2,CEP170,ADAMTS16,GTF2H2C,CEND1,IFITM1,SRRM2-AS1,AC091167.3,RP11-30P6.1,RP5-956O18.3,RP11-137H2.4,COL6A4P1,RP5-836N10.1,VN1R20P,RP11-381E24.1,TET2-AS1,RP11-361I14.2,RP11-732A19.9,CTD-2329K10.1,LA16c-385E7.1,RN7SL15P,SH3GL1P2,MIR3942,RP11-820I16.1

383L7.1,RN7SL15P,SH3GLB2,MIR3942,RP11-820I16.1, HMGB2P1,RP11-479O17.10
ARHGAP31,PEX3,DPP8,CPNE3,KDELR3,A4GNT,RIBC2,NCBP1,SLC25A26,ANKAR,CERS3,CCDC28B,PRORSD1P,NRG4,FAM26F,ZNF789,NFKBIL1,Y_RNA,RP1-13D10.2,LINC00205,AC002117.1,RP13-216E22.4,MED4-AS1,ZRANB2-AS1,AD000090.2,RP11-206L10.9,RP11-353N4.2,RP11-499P20.2,TMEM161B-AS1,AC008592.4,RP11-15A1.2,CTD-2639E6.9
MCM10,RRP15,EPN2,MTMR3,CPSF6,RBBP5,FBXO30,PAICS,CAPN11,RNF144B,HAUS2,KIF21A,FAM222A,CTDSPL,HNRNPU,TOMM70A,RIBC1,RRP1B,RBP7,FUBP1,S100Z,C17orf66,NUDT4,DSG4,MED16,OR10A6,GCNT4,TMEM139,ZNF320,C11orf72,CXorf38,ZNF566,ZNF197,TNFRSF18,MAGI2,VWC2,GLRA4,AC104472.1,UBE2Q2P2,AC073621.2,AC073850.6,FGF12-AS2,AC073342.12,RP11-557H15.4,RP11-640M9.1,RN7SL331P,AP000322.53,RP11-51J9.4,RP11-1055B8.4,RP11-135L13.4,RP11-64C12.8
TNMD,CX3CL1,DAPK2,HEBP2,TRAF3IP2,GYG2,LIPE,SEPHS1,FMO2,APMAP,SLC6A2,FAH,ETFB,SH3D19,CPT1A,TMED5,ITGB1BP1,KCNIP2,CAT,WIPF3,ACVR1C,PCK1,ARHGEF6,SLC7A10,INPP5K,KL,TCN1,ADAM19,SDS,CD36,PPP1R1A,TTLL4,SLC19A3,PTN1

SK,KL,TCN1,ADAM19,SD3,CD36,PPP1R1A,TTLL4,SLC19A3,KIN1 ,ETFA,ADAMTS18,SELENBP1,CDKN2B,TM7SF2,FLI1,PDE3B,PL OD2,RWDD2B,NAA11,RPUSD3,C2CD2,HPD,PFKFB1,FBXO27,CC DC51,CTSB,SUN1,NIPSNAP3B,AQP7,ZNF219,GPT2,PLIN1,ACAA2 ,GPD1,PLIN4,ANGPTL4,GLYCTK,GSG1L,MRAP,FABP4,PFKFB3, MUC7,AQPEP,DCTN2,FOXG1,CIDEA,PLA2G16,BOK,RPLP2,PNP LA2,COX14,ADIPOQ,ABAT,TUSC5,NAT8L,CIDEC,DHRS4L2,MAO A,MAN2A2,VKORC1L1,KCNRG,NUDT16,GJC2,LINC00222,PCDH A7,AC022007.5,MIR135A1,ZNF259P1,KCNIP2-AS1,AC022596.6,ADIPOQ-AS1,RP11-445L13__B.3,RP1-28O10.1,AC008738.1,VN1R108P,RP11-573D15.1,RP5-1172A22.1,RP1-293L6.1,LINC00263,TRHDE-AS1,AC159540.2,VWFP1,GLYCTK-AS1,CEBPA,RP11-768F21.1,CTD-2589H19.4,RP13-884E18.2,RP11-1101K5.1,PAICSP4,AP006621.8,RP11-317P15.5,RP11-663N22.1
HIVEP2,LAMA3,SEPHS1,ARHGAP28,DHX32,GGA1,EIF3D,PSMD7 ,GPI,URGCP,XPNPEP1,PPP1R9B,SMURF2,DDX25,NR5A1,TP53B P2,PIK3R1,SYBU,CDYL,NCAM2,DHRS4,G6PD,ZER1,SHANK1,HA AO,SH3TC2,PACS1,L3MBTL3,LINC00162,RP11-536C5.7,RP11-213G2.2,AC002401.1,MTX1P1,RP11-247I13.11,LINC00461,RP11-281P23.2,RP11-10A14.4,RP11-578O24.2,FTLP14,AC005702.1,RP11-138E2.1,RP11-216P16.2
BTK,HERPUD1,PRDM1,KCNAB2,ZFAND6,DERL3,SRRD,ACSS3,L AX1,ZBP1,RGS13,TEC,DUOXA2,RPL11,UGCG,LPCAT1,GFI1B,RN F187,SHCBP1,AP006621.1,PIDD,NUGGC,IGHA1,FIS1,IGLC6,RPL 32P1,RP11-162O12.2,LINC00568,GS1-124K5.11,LINC00582,AC007285.7,AC005162.5, RP11-181G12.4,LINC01010,RPS20P21, H2AFJ,RP11-510M2.2, RP11-1084E5.1,AP006621.5,AC091171.1,RP11-554D14.4,RP11-42I10.1,RP11-61A14.3,RP11-325K4.3,RP11-174G6.5,RP11-849F2.8,RP4-713A8.1,STAG3L5P-PVRIG2P-PILRB

RC3H2,TDRD3,GPATCH2L,IL5RA,EZR,TFIP11,MIB1,CD79A,EPB41L5,SLC1A4,STAT5A,CASZ1,VSTM2L,SPIRE1,KLF4,NAA30,TBX19,RNF145,AZGP1,SCIMP,PPP1R32,VANGL2,LEO1,LMAN2,SERPINA6,NAT1,NDUFA11,SOX11,TSSK6,PCED1B,CRELD2,LCN12,CCDC157,NKAPL,TMEM240,IGLV2-23,IGLV3-19,IGLC3,CCL27,HLA-F-AS1,RP11-216N14.5,AC068587.2,RP11-557J10.4,CTD-2240H23.2,KB-1460A1.5,LA16c-431H6.6,RP11-283I3.6,RP11-597M12.1,RP11-694I15.7,RP4-734G22.3
PREX2,CD82,MARCH2,INTS10,TPD52L1,MORN1,HSDL2,CHST8,FGD3,IL17B,BTBD3,PRSS23,ANKFN1,ZKSCAN2,SUSD3,ALDH16A1,HDAC11,GPD1,EMR1,CTDNEP1,SRGAP3,SFTA2,AC074391.1,AL021068.1,RP11-553A21.3,RP4-669P10.16,LL0XNC01-237H1.3,DPY19L2P4,AC007750.5,KRT8P36,RP11-368I23.2,RP11-16P20.3,FMR1-AS1
MBTD1,AGA,CHI3L2,FNDC3B,GRHL2,CRLS1,ESR1,DHRS7,HTATSF1,DNAJB6,GATA3,ATE1,STC2,MOGS,PDCL3,SLC1A4,NR5A2,IPO13,STAT5A,TRPV5,EPS15L1,YWHAH,RAF1,HRASLS2,GLCE,C1RL,GRTP1,IGLON5,UCK2,TNFRSF21,RNF44,RASSF3,C17orf103,SH3RF2,PLXDC1,ADCY9,C1orf50,MOCS2,FBP1,TAF1D,DEGS2,PLA2G4F,C3orf33,IRX5,IRX3,SETD3,C1orf64,PIP5K1C,EIF4EBP1,HUS1B,ZKSCAN7,CALM1,CAPN8,SPINK9,SNORA40,LINC00277,RP11-223A3.1,ATP8A2P2,AK3P3,RP11-5P18.5,LINC00941,KIFC1,RP11-69L16.4,RP1-93H18.1,RP11-

64D22.2,RGAG1,CTB-33O18.1,RP11-676M6.1,POLG2,AC040173.1,RP11-114F10.2,LINC00567,AC009133.20,RP11-106E15.1,CTD-2206N4.4,CTD-3214H19.6,CTD-3099C6.11,CTD-2376I4.2,RP11-383I23.2
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ATG10

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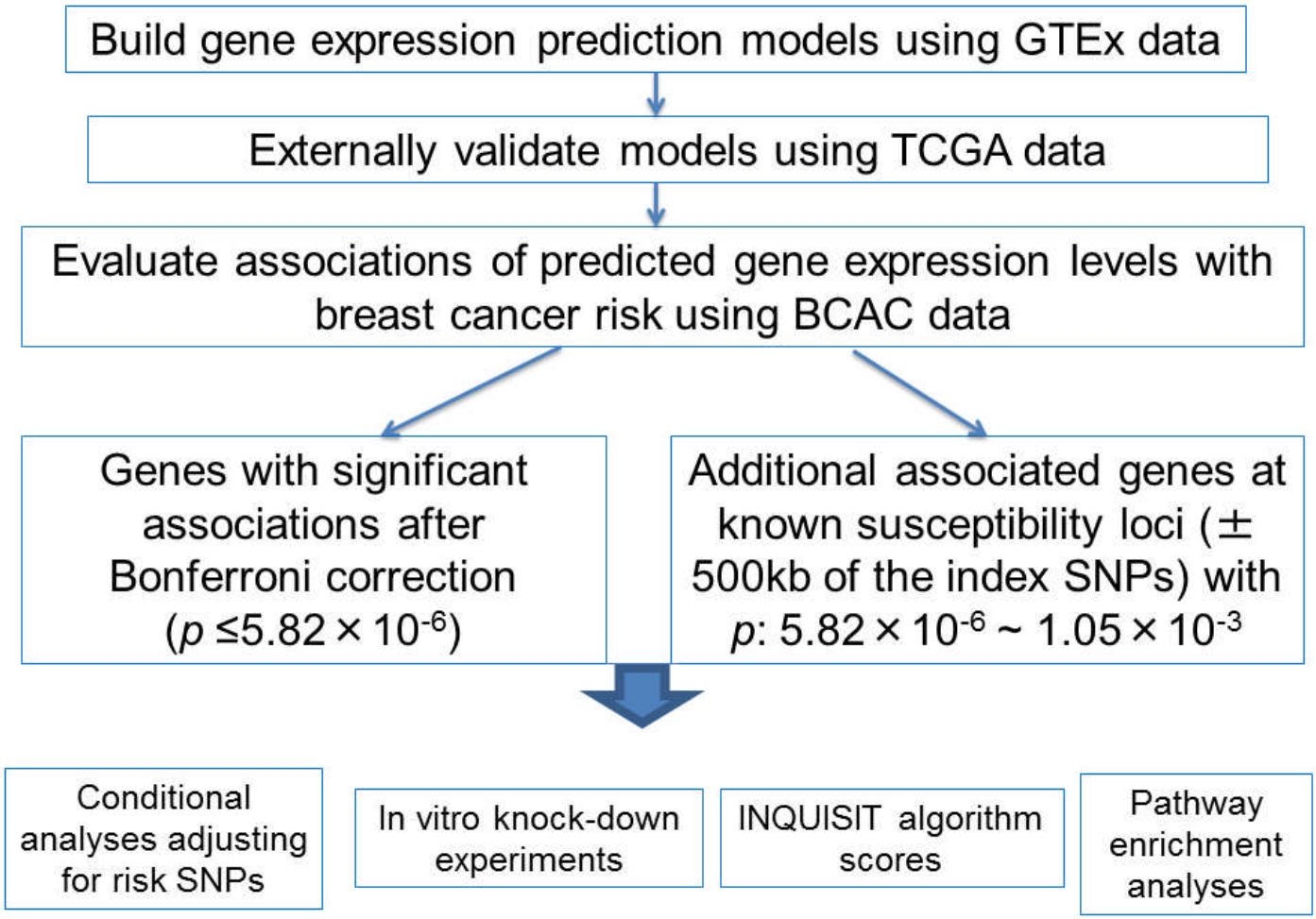
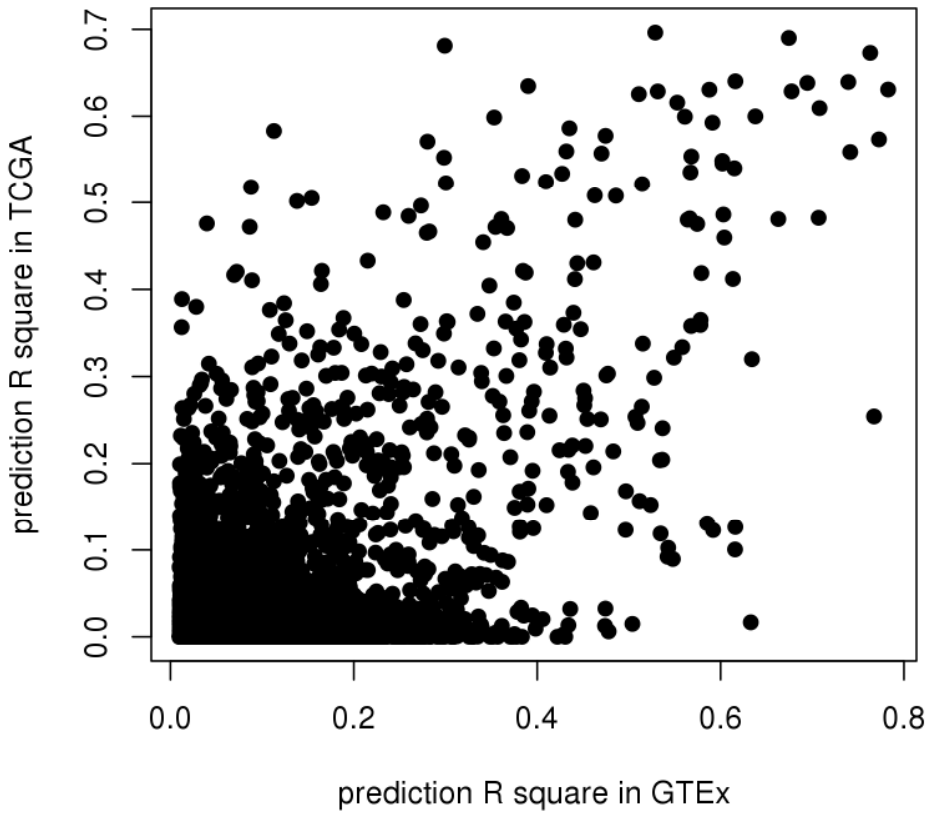


Supplementary Figure 1

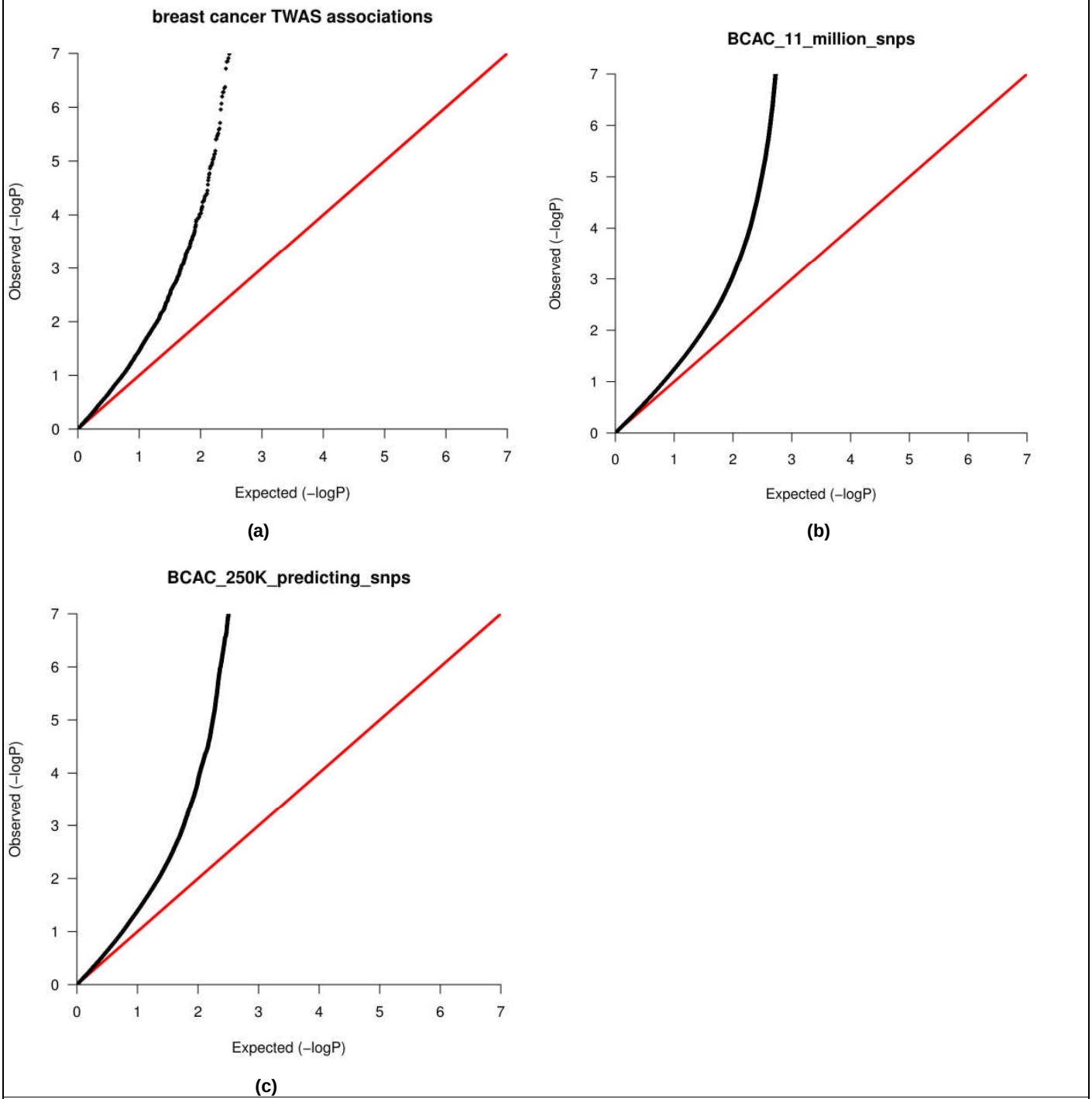
Study design flow chart



Supplementary Figure 2

Performance of expression prediction models in GTEx and TCGA datasets for genes with at least 10% correlation in GTEx data

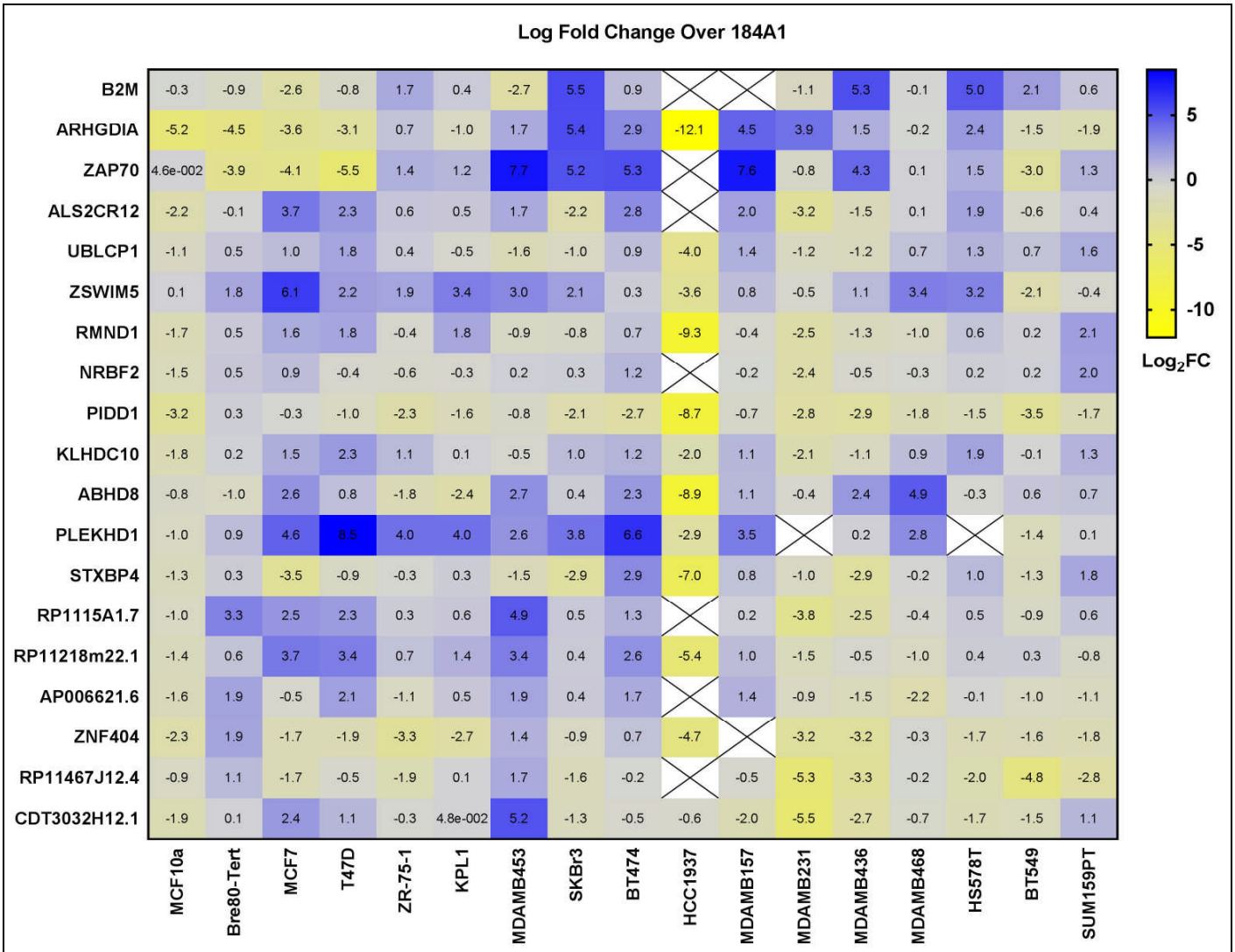
The x axis represents the prediction performance (R^2) in GTEx dataset (n=67). The y axis represents the prediction performance in TCGA dataset (n=86). Each dot represents the expression prediction model for one gene. There is a trend that genes with a high internal prediction performance in GTEx data also have a high external prediction performance in TCGA data (Pearson's correlation coefficient: 0.55).



Supplementary Figure 3

Quantile-quantile plots

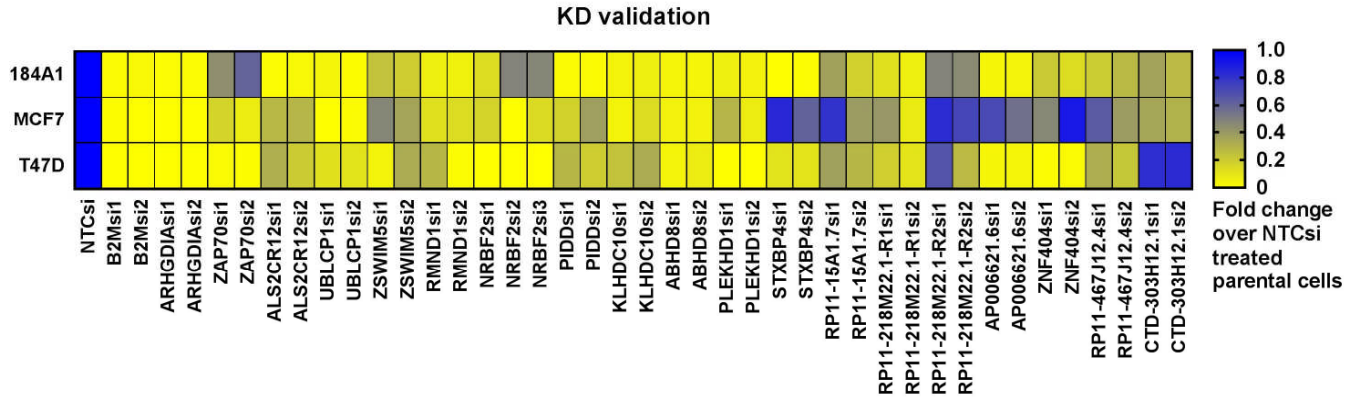
(a) Quantile-quantile plot of P values in –log scale of associations between genetically predicted expression levels of 8,597 genes and breast cancer risk; (b) Quantile-quantile plot of P values in –log scale of associations between all 11.8 million SNPs and breast cancer risk in BCAC; (c) Quantile-quantile plot of P values in –log scale of associations between the over 250,000 SNPs predicting expression levels of the 8,597 genes and breast cancer risk in BCAC



Supplementary Figure 4

Heat map of log fold change (FC) of selected genes normalized to expression levels in 184A1 breast cells

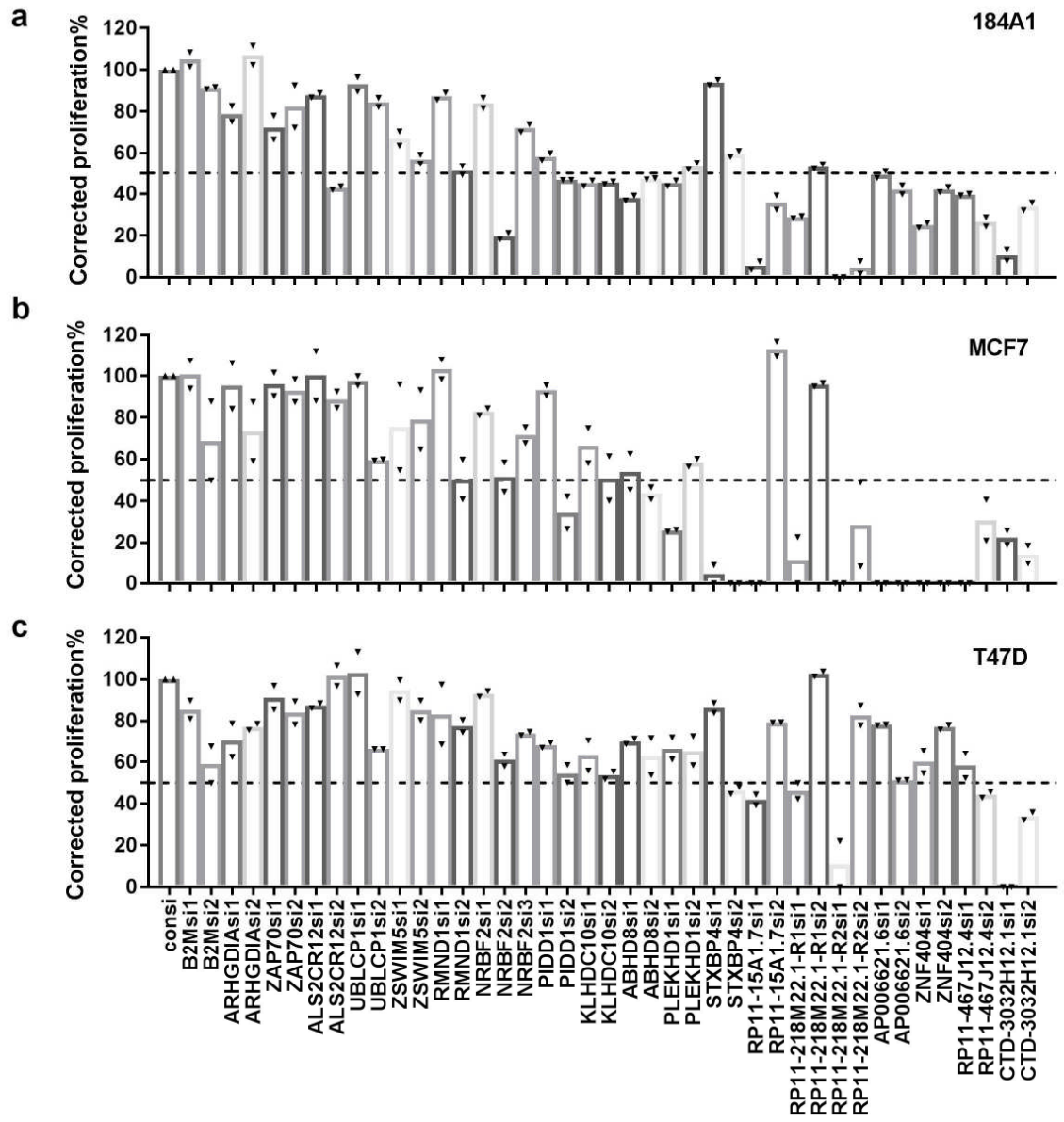
Two or three primer sets were designed for each gene (y-axis) and mRNA levels quantified by qPCR in indicated cells lines (x-axis), including 184A1. The FC of genes normalized to that in 184A1 = mRNA level in indicated cells / mRNA level in 184A1. The log2FC over 184A1 is depicted as a heat map. An X represents “not detectable” with all primer sets. The experiment was repeated independently twice with similar results.



Supplementary Figure 5

Validation of knockdown

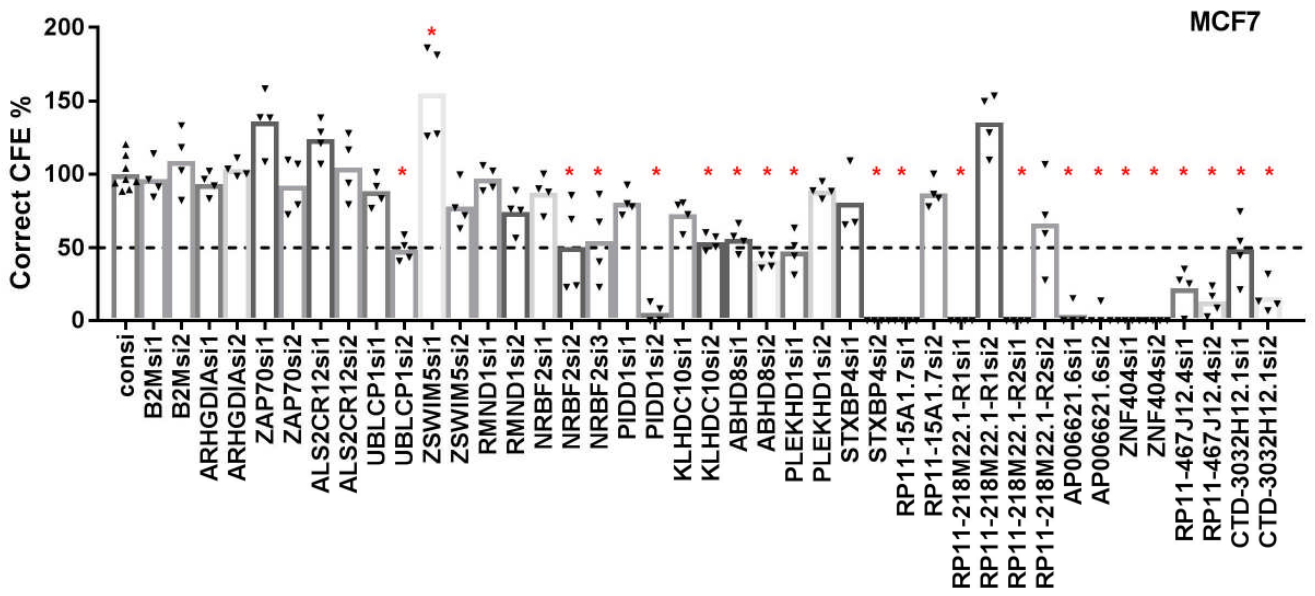
184A1, MCF7 and T47D cells, transfected with the indicated siRNAs, were harvested after 36 hours for qPCR analysis to assess knockdown efficiency. The fold changes over NTCsi-transfected parental cells were plotted. The experiment was repeated three times independently with similar results.



Supplementary Figure 6

Proliferation in breast cells using two independent siRNAs (related to Figure 2(a))

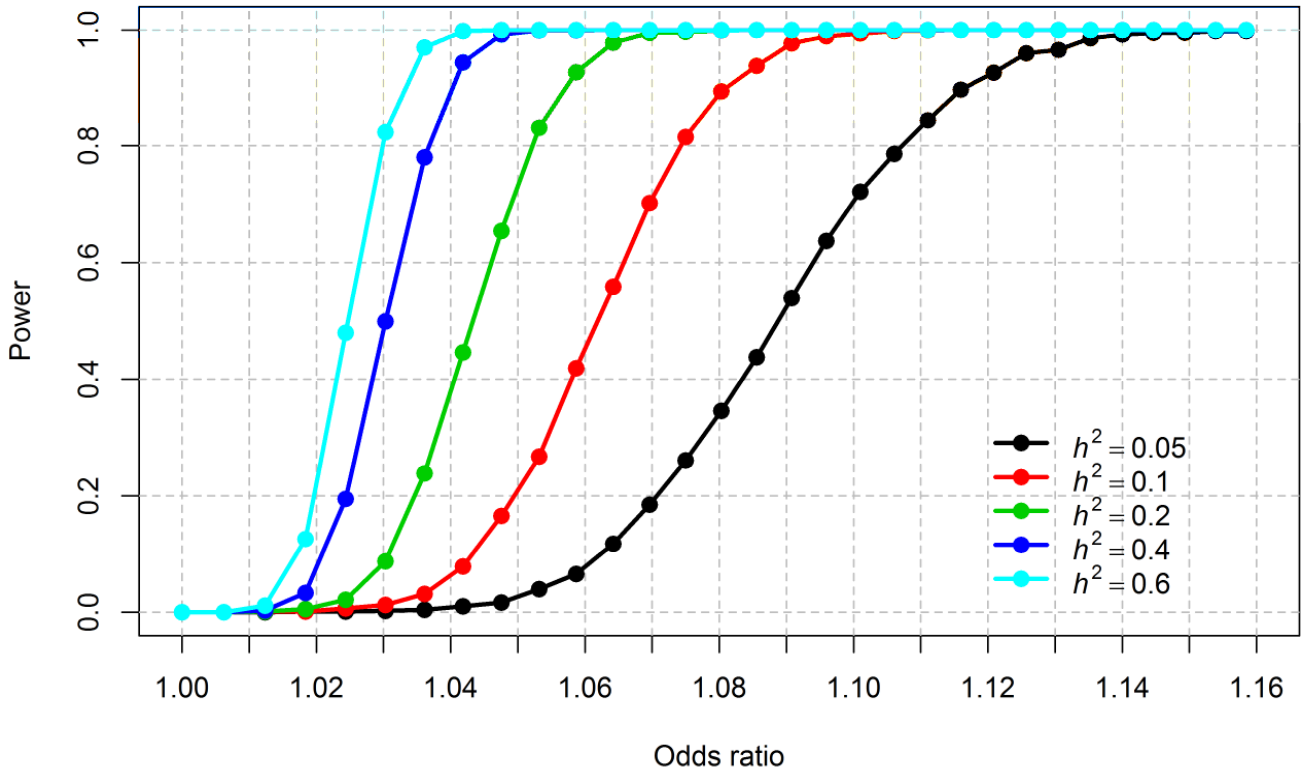
(a) 184A1, **(b)** MCF7 or **(c)** T47D cells were transfected with indicated siRNAs over seven days and phase-contrast images collected using an IncuCyte ZOOM. Each cell proliferation time-course was normalized to the baseline confluency and analyzed in GraphPad Prism. Corrected proliferation % = 100 +/- (relative proliferation in indicated siRNA - proliferation in control siRNA (consi))/knockdown efficiency.



Supplementary Figure 7

Colony formation efficiency in MCF7 cells using two independent siRNAs (related to Fig 2B)

MCF7 cells were transfected with indicated siRNAs, then reseeded after 16 hours for colony formation (CF) assays. At day 14, colonies were fixed with methanol, stained with crystal violet, scanned and batch analyzed by ImageJ. Corrected CF efficiency (CFE) % = 100 +/- (relative CFE in indicated siRNA - CFE in control siRNA (consi))/knockdown efficiency. Error bars, SD (*N*=4). *P*-values were determined by one-way ANOVA followed by Dunnett's multiple comparisons test: **P*-value < 0.05.



Supplementary Figure 8

Power calculation of the TWAS analysis

The simulation analysis is based on 122,977 cases and 105,974 controls. The gene expression was generated from the empirical distribution of predicted gene expression levels in the BCAC. Statistical power was calculated at $P<5.82\times10^{-6}$ (the significance level used in main TWAS analyses) according to cis-heritability (h^2) which we aim to capture using gene expression prediction models (R^2). The figure shows results per one standard deviation increase (or decrease) in the gene expression based on 1000 replicates.

Supplementary Table 1. Internal performance of gene expression prediction models built using GTEx data

Prediction performance (R^2)	**All**	**Protein**	**lncRNAs**	**miRNAs**	**Others***
Number of genes	15,148	10,483	4,277	68	320
0.01[#]	12,824	8,874	3,628	57	265
0.04	7,655	5,244	2,200	38	173
0.09	3,818	2,601	1,106	19	92
0.16	1,573	1,035	479	8	51

Protein: protein coding genes; lncRNAs: long non-coding RNAs; miRNAs: microRNAs

* Including processed transcripts, immunoglobulin genes, and T cell receptor genes

[#] The R^2 of 0.01 is the internal prediction performance threshold according to which the prediction models were retained for external evaluation in the TCGA data

Supplementary Table 5. In-depth individual level association analyses of predicted expression of 41 identified genes with breast cancer risk in iCOGS and OncoArray datasets identified similar results to those obtained using summary statistics

Gene name	iCOGS dataset individual level analysis (n=84,740)		iCOGS dataset summary statistics analysis (n=89,677)		OncoArray dataset individual level analysis (n=112,133)		OncoArray dataset summary statistics analysis (n=106,776)	
	z-score[a]	*p*-value[a]	z-score[a]	*p*-value[a]	z-score[b]	*p*-value[b]	z-score[b]	*p*-value[b]
Table 1								
ZSWIM5	3.86	1.12×10^{-4}	4.32	1.57×10^{-5}	3.50	4.73×10^{-4}	2.98	0.003
LRRC3B	-4.76	1.95×10^{-6}	-4.89	1.02×10^{-6}	-7.44	1.04×10^{-13}	-7.48	7.19×10^{-14}
SPATA18	-2.02	0.04	-2.59	0.01	-2.89	3.90×10^{-3}	-3.09	0.002
KLHDC10	3.53	4.12×10^{-4}	4.39	1.16×10^{-5}	2.39	0.02	2.15	0.03
MIR31HG	-2.87	4.07×10^{-3}	-2.90	0.004	-4.99	6.11×10^{-7}	-4.35	1.35×10^{-5}
RIC8A	-3.11	1.86×10^{-3}	-3.12	0.002	-4.15	3.26×10^{-5}	-3.28	0.001
B3GNT1	-3.68	2.35×10^{-4}	-5.00	5.83×10^{-7}	-3.18	1.49×10^{-3}	-2.70	0.007
RP11-218M22.1	2.82	4.82×10^{-3}	3.33	8.82×10^{-4}	3.58	3.47×10^{-4}	3.84	1.22×10^{-4}
GALNT16	-5.07	3.93×10^{-7}	-6.17	6.82×10^{-10}	-4.70	2.62×10^{-6}	-4.45	8.74×10^{-6}
PLEKHD1	2.92	3.50×10^{-3}	3.96	7.43×10^{-5}	5.73	1.01×10^{-8}	5.21	1.85×10^{-7}
MAN2C1	-3.24	1.19×10^{-3}	-3.49	4.88×10^{-4}	-3.69	2.24×10^{-4}	-4.08	4.47×10^{-5}
CTD-2323K18.1	-2.91	3.56×10^{-3}	-2.62	0.009	-3.63	2.88×10^{-4}	-3.69	2.23×10^{-4}
Table 2								
RP11-439A17.7	-3.37	7.61×10^{-4}	-3.39	6.90×10^{-4}	-3.51	4.50×10^{-4}	-4.35	1.37×10^{-5}
ALK	3.27	1.06×10^{-3}	3.23	0.001	4.51	6.62×10^{-6}	3.84	1.23×10^{-4}
PRSS46	-3.22	1.26×10^{-3}	-3.51	4.41×10^{-4}	-5.00	5.80×10^{-7}	-4.33	1.51×10^{-5}
RP11-114I8.4	-3.22	1.28×10^{-3}	-3.15	0.002	-3.77	1.65×10^{-4}	-4.20	2.66×10^{-5}
UBLCP1	2.17	0.03	3.12	0.002	5.10	3.44×10^{-7}	4.72	2.34×10^{-6}
RP11-32D16.1	-2.68	7.31×10^{-3}	-3.66	2.51×10^{-4}	-4.63	3.63×10^{-6}	-3.75	1.75×10^{-4}
BTN3A2	1.51	0.13	2.74	0.006	3.65	2.65×10^{-4}	3.16	0.002
RP11-73O6.3	-1.62	0.11	-2.24	0.03	-5.72	1.08×10^{-8}	-5.34	9.31×10^{-8}
AP006621.6	4.29	1.82×10^{-5}	3.92	8.75×10^{-5}	3.45	5.58×10^{-4}	3.58	3.40×10^{-4}

RPLP2	2.93	3.44×10^{-3}	2.77	0.006	3.39	6.92×10^{-4}	3.43	5.93×10^{-4}
CTD-3051D23.1	-2.83	4.62×10^{-3}	-3.36	7.85×10^{-4}	-2.64	8.39×10^{-3}	-2.60	0.009
RP11-467J12.4	4.78	1.71×10^{-6}	5.41	6.28×10^{-8}	5.63	1.83×10^{-8}	5.75	8.73×10^{-9}
CTD-3032H12.1	3.79	1.50×10^{-4}	2.95	0.003	3.33	8.60×10^{-4}	2.93	0.003
LRRC37A	-3.07	2.11×10^{-3}	-3.08	0.002	-3.75	1.77×10^{-4}	-4.13	3.56×10^{-5}
KANSL1-AS1	-3.12	1.83×10^{-3}	-3.17	0.002	-3.53	4.10×10^{-4}	-3.83	1.28×10^{-4}
CRHR1	-2.67	7.59×10^{-3}	-2.81	0.005	-3.35	7.94×10^{-4}	-3.58	3.39×10^{-4}
HAPLN4	-4.73	2.26×10^{-6}	-5.10	3.46×10^{-7}	-5.87	4.44×10^{-9}	-5.49	4.01×10^{-8}
RP11-15A1.7	3.57	3.54×10^{-4}	4.26	2.00×10^{-5}	4.71	2.45×10^{-6}	3.65	2.59×10^{-4}
Table 3								
KLHDC7A	-2.87	4.06×10^{-3}	-3.53	4.11×10^{-4}	-4.51	6.54×10^{-6}	-4.69	2.77×10^{-6}
ALS2CR12	2.47	0.01	2.80	0.005	5.09	3.53×10^{-7}	4.98	6.25×10^{-7}
CASP8	-3.72	2.03×10^{-4}	-3.63	2.78×10^{-4}	-5.85	4.98×10^{-9}	-5.97	2.42×10^{-9}
ATG10	-4.55	5.28×10^{-6}	-5.83	5.60×10^{-9}	-4.04	5.44×10^{-5}	-3.00	0.003
ATP6AP1L	-3.33	8.80×10^{-4}	-4.24	2.20×10^{-5}	-3.72	2.02×10^{-4}	-2.40	0.02
L3MBTL3	-1.77	0.08	-2.38	0.02	-5.77	8.06×10^{-9}	-5.42	5.89×10^{-8}
RMND1	2.44	0.01	2.76	0.006	3.64	2.68×10^{-4}	3.14	0.002
SNX32	3.56	3.70×10^{-4}	3.80	1.45×10^{-4}	2.99	2.76×10^{-3}	2.41	0.02
RCCD1	-3.49	4.92×10^{-4}	-4.08	4.56×10^{-5}	-5.76	8.26×10^{-9}	-5.58	2.36×10^{-8}
STXBP4	3.53	4.22×10^{-4}	4.01	6.05×10^{-5}	5.26	1.42×10^{-7}	4.77	1.85×10^{-6}
ZNF404	4.76	1.91×10^{-6}	5.28	1.28×10^{-7}	5.97	2.44×10^{-9}	4.76	1.96×10^{-6}

[a] logistic regression analyses adjusting for study, the first eight principal components, and a principal component derived specifically for the study LMBC (set to zero for all other studies).
[b] logistic regression analyses adjusting for country and the first ten principal components.

Supplementary Table 6. INQUISIT scores of the identified genes showing a significant association with breast cancer risk in the TWAS ($p \leq 5.82 \times 10^{-6}$)

Gene	Distal	Promoter	GTEx eQTL
From Table 1			
ZSWIM5	none	none	
LRRC3B	none	none	
SPATA18	none	none	
UBD	0.05	none	
KLHDC10	none	none	
MIR31HG	none	none	
RIC8A	none	none	
B3GNT1	none	none	
RP11-867G23.10	none	none	
RP11-218M22.1	none	none	
GALNT16	none	none	
PLEKHD1	none	none	
MAN2C1	none	none	
CTD-2323K18.1	none	none	
From Table 2			
RP11-439A17.7	none	none	yes
NUDT17	3	none	
ANKRD34A	1	none	
ALK	none	none	
PRSS46	none	none	
RP11-114I8.4	none	none	
RP11-53O19.1	none	none	
UBLCP1	none	none	
RP11-32D16.1	none	none	
BTN3A2	none	none	yes
RP11-73O6.3	none	none	
AP006621.6	none	none	yes

RPLP2	1	none	
CTD-3051D23.1	none	none	
RP11-467J12.4	none	none	
CTD-3032H12.1	none	none	
LINC00671	none	none	
LRRC37A2	1	none	
LRRC37A	1	none	
KANSL1-AS1	3	none	
CRHR1	1	none	
HAPLN4	1	none	
RP11-15A1.7	None	none	
From Table 3			
KLHDC7A	none	3	
ALS2CR12	1	none	
CASP8	3	none	
ATG10	3	4	
ATP6AP1L	0.1	none	
L3MBTL3	2	2	
RMND1	4	none	
SNX32	2	none	
RCCD1	5	none	
STXBP4	1	none	
ZNF404	2	none	

The detailed methodology of INQUISIT algorithm scores was described in Michailidou, K. *et al*[1]

Supplementary Table 8. Cell line and media information.

Cell Line	Media constituents
MCF10A	DMEM/F12 + 5% Horse Serum + 20ng/mL EGF + 0.5µg/mL Hydrocortisone + 100ng/mL Cholera Toxin + 10 µg/mL Insulin from bovine pancreas + 1% Penicillin-Streptomycin
Bre80-Tert	DMEM/F12 + 5% Horse Serum + 20ng/mL EGF + 0.5µg/mL Hydrocortisone + 100ng/mL Cholera Toxin + 10 µg/mL Insulin from bovine pancreas + 1% Penicillin-Streptomycin
184A1	MEGM + BPE 52ug/mL + HC 500ng/mL + EGF 10ng/ml + I 5ug/ml + transferrin 5ug/mL + cholera toxin 1ng/mL
ZR751	RPMI-1640 + 10% Fetal Bovine Serum + 1% Penicillin-Streptomycin + 10 µg/mL Insulin from bovine pancreas
MCF7	RPMI-1640 + 10% Fetal Bovine Serum + 1% Penicillin-Streptomycin
KPL1	DMEM + 10% Fetal Bovine Serum + 1% Penicillin-Streptomycin
T47D	RPMI-1640 + 10% Fetal Bovine Serum + 1% Penicillin-Streptomycin
SKBR3	DMEM + 10% Fetal Bovine Serum + 1% Penicillin-Streptomycin
BT474	RPMI-1640 + 10% Fetal Bovine Serum + 1% Penicillin-Streptomycin
MDA-MB-453	DMEM/F12 + 20% Fetal Bovine Serum + 1% Penicillin-Streptomycin + 10 µg/mL Insulin from bovine pancreas
MDA-MB-231	DMEM + 10% Fetal Bovine Serum + 1% Penicillin-Streptomycin
MDA-MB-436	DMEM + 10% Fetal Bovine Serum + 1% Penicillin-Streptomycin

BT549	RPMI-1640 + 10% Fetal Bovine Serum + 1% Penicillin-Streptomycin
MDA-MB-157	DMEM + 10% Fetal Bovine Serum + 1% Penicillin-Streptomycin
HCC1937	RPMI-1640 + 10% Fetal Bovine Serum + 1% Penicillin-Streptomycin
HS578T	DMEM + 10% Fetal Bovine Serum + 1% Penicillin-Streptomycin
SUM159PT	RPMI-1640 + 10% Fetal Bovine Serum + 1%Penicillin-Streptomycin
MDA-MB-468	DMEM + 10% Fetal Bovine Serum + 1% Penicillin-Streptomycin

Supplementary Table 9. siRNA sequences.

Name	Sense sequence (5'-3')	Antisense sequence (5'-3')
RMND1-1	CCACGGAUAUGUUGAAGUATT	UACUUCAACAUAUCCGUGGGA
RMND1-2	CAAACCAAAUCUGUUGGGUUCUAAA	UUUAGAACCCAACAGAUUUGGUUUG
KLHDC10-1	CAACCUAUAUGUGUUUGGAGGUUAU	AUAACCUCCAAACACAUAUAGGUUG
KLHDC10-2	GAGAUAUCUGGAAGUUGAAUCUGCA	UGCAGAUUCAACUUCCAGAUAUCUC
ZSWIM5-1	GGGAAAGUGAAAGACUACUCUUUAA	UUAAAGAGUAGUCUUUCACUUUCCC
ZSWIM5-2	CCUCAUUGGCCAUGAGCCAUCUUAA	UUAAGAUGGCUCAUGGCCAAUGAGG
UBLCP1-1	GCACCUAAAUCGUGAUAAATT	UUUAUCACGAUUUAGGUGCGC
UBLCP1-2	CAGGAGUAUUCAGUGACCACACUUU	AAAGUGUGGUCACUGAAUACUCCUG
PLEKHD1-1	UCAAAGAGAGCUUUCUGCUUUACUA	UAGUAAAGCAGAAAGCUCUCUUUGA
PLEKHD1-2	AAGAUGCCUUAAGGGUGUAGAACA	UGUUCUACACCCUUAAGGCAUCUUG
ALS2CR12-1	AACUCCACAGGGAGUUCCAAGCUAA	UUAGCUUGGAACUCCCUGUGGAGUU
ALS2CR12-2	CAGCAAGGCAAGAAGAGACUAAUAA	UUAUUAGUCUCUUCUUGCCUUGCUG
STXBP4-1	(CCUGGAGGAGACUGUUAUA)dTdT	(UAUAACAGUCUCCUCCAGG)dAdA
STXBP4-2	(GGACCUCAAGCCUCAACAU)dTdT	(AUGUUGAGGCUUGAGGUCC)dAdT
ZNF404-1	UGCGUACCAUCAGGAGACAUGGAAA	UUUCCAUGUCUCCUGAUGGUACGCA
ZNF404-2	GGGAAACGUUUAGAUUAUAUCGACA	UGUCGAUAUAAUCUAAACGUUUCCC
PIDD-1	GACUGUUCCUGACCUCAGAtt	UCUGAGGUCAGGAACAGUCtg
PIDD-2	AGGGCAGAAUCUGCUUUGUCUUCUA	UAGAAGACAAAGCAGAUUCUGCCCU
NRBF2-1	UGUGAAAUGCGCUGCGUAUUU	AUACGCAGCGCAUUUCACAUU
NRBF2-2	CCGGAGGAGGAAGUGGUGAGGUUGU	ACAACCUCACCACUUCCUCCUCCGG
NRBF2-3	AGGAAGUGGUGAGGUUGUUGCUCCU	AGGAGCAACAACCUCACCACUUCCU
ABHD8-1	GAGCAAUCUUCAAGCGCUAUGCCAA	UUGGCAUAGCGCUUGAAGAUUGCUC
ABHD8-2	CAUUCCUACGGUGUCUCUUUCUGCA	UGCAGAAAGAGACACCGUAGGAAUG
RP11-218M22-R1-1	UGAGCGCAGGAACCAUGGUCUUCAU	AUGAAGACCAUGGUUCCUGCGCUCA
RP11-218M22-R1-2	CGCAGGAACCAUGGUCUUCAUUGCU	AGCAAUGAAGACCAUGGUUCCUGCG
RP11-218M22-R2-1	CCAGUGGGUUUGGAUAUAAUCCUGA	UCAGGAUUAUAUCCAAACCCACUGG
RP11-218M22-R2-2	CAGACUGCGAGACAAUCUCUCUUUA	UAAAGAGAGAUUGUCUCGCAGUCUG
AP006621.6-1	GGGUACCUUCACCUGGGCGUCAGAA	UUCUGACGCCCAGGUGAAGGUACCC

AP006621.6-2	UCACCUGGGCGUCAGAAGCACUUGA	UCAAGUGCUUCUGACGCCCAGGUGA
RP11-467J12.4-1	CACCAUAUCAUGGUUCCCACUAGCA	UGCUAGUGGGAACCAUGAUAUGGUG
RP11-467J12.4-2	UAUGAGAGUUCCAGUUGCUCCACAA	UUGUGGAGCAACUGGAACUCUCAUA
RP11-15A1.7-1	CACCCUCCUCAUACUUCCGUAGUUU	AAACUACGGAAGUAUGAGGAGGGUG
RP11-15A1.7-2	GGAAUCCACCUAAGUGUCUAUCAAU	AUUGAUAGACACUUAGGUGGAUUCC
CTD-3032H12.1-1	CAAGCUCCCGAGGCGAUCUGCUGUU	AACAGCAGAUCGCCUCGGGAGCUUG
CTD-3032H12.1-2	AGGCCCAAGUCGCAGUUCUCGUGAA	UUCACGAGAACUGCGACUUGGGCCU
B2M-1	CCAGCGUACUCCAAAGAUUTT	AAUCUUUGGAGUACGCUGGTT
B2M-2	GGTTTACTCACGTCATCCATT	TGGATGACGTGAGTAAACCTT
ARHGDIA-1	CCCGUCUAACCAUGAUGCCUUAACA	UGUUAAGGCAUCAUGGUUAGACGGG
ARHGDIA-2	CCUUAACAUGUGGAGUGUACCGUGG	CCACGGUACACUCCACAUGUUAAGG
ZAP70-1	UAACCUCCUCAUAGCUGACAUUGAA	UUCAAUGUCAGCUAUGAGGAGGUUA
ZAP70-2	CCGAAUGCAUCAACUUCCGCAAGUU	AACUUGCGGAAGUUGAUGCAUUCGG

Supplementary Table 10. Literature reported link between genes identified in our study that have not been reported from eQTL and/or following functional studies as target genes of risk variants (Tables 1-2) and breast cancer

Gene	Reported link with breast cancer	Study type	Consistency with the direction of effect identified in our study	PMID of literature
Table 1				
ZSWIM5	NA	NA	NA	NA
LRRC3B	inhibits bupivacaine-induced breast cancer cell invasion	*In vitro*	consistent	29085514
	reduced expression in breast cancer tissues compared with breast fibroma tissues; low gene expression associated with higher tissue grade	Human tissues		24839112
	methylated and/or deleted in ~32% breast carcinoma samples	Human tissues		22321817
SPATA18	downregulated ~ 5-folds in human ductal breast carcinomas compared with normal breast samples	Human tissues	consistent	21300779; 16473279
UBD	inhibits growth in MCF-7 breast carcinoma cells	*In vitro*	consistent	12170760
	increased expression in breast cancer tissues compared with surrounding tissues; expression correlated with triple-negative breast cancer (TNBC)	Human tissues	inconsistent	26185453
KLHDC10	NA	NA	NA	NA
MIR31HG	down-regulated in TNBC cell lines of basal subtype; heavily methylated in the TNBC cell lines	*In vitro*	consistent	22289355
	increased expression in breast cancer tissues compared with normal control; expression associated with advanced pathologic stage and tumor size; knockdown decreases breast cancer cell proliferation, induces apoptosis, inhibits migration/invasion and impedes tumorigenesis	*In vitro, in vivo,* and human tissues	inconsistent	24631686
RIC8A	undergoes a classical double-hit genetic inactivation in a breast	*In vitro* and *in*	consistent	19432969

	cancer cell line; loss of expression in a subgroup of aggressive *TP53* mutant breast cancers	*vivo*		
B3GNT1	NA	NA	NA	NA
RP11-867G23.10	NA	NA	NA	NA
RP11-218M22.1	NA	NA	NA	NA
GALNT16	NA	NA	NA	NA
PLEKHD1	NA	NA	NA	NA
MAN2C1	NA	NA	NA	NA
CTD-2323K18.1	NA	NA	NA	NA
Table 2				
RP11-439A17.7	NA	NA	NA	NA
NUDT17	NA	NA	NA	NA
ANKRD34A	NA	NA	NA	NA
ALK	overexpressed in 36% of breast cancer patients; gene amplification present in 13.3 % of cases; overexpression associated with aggressive behavior	Human tissues	consistent	26384210
	amplified in a large proportion of Inflammatory Breast Cancers (IBC), a highly aggressive subtype of breast cancer	*In vitro* and human tissues		22215853
	copy number gain observed in 47.2% of IBC patients; copy number gain associated with poorer recurrence free survival	Human tissues		25803816
PRSS46	NA	NA	NA	NA
RP11-114I8.4	NA	NA	NA	NA
RP11-53O19.1	NA	NA	NA	NA
UBLCP1	NA	NA	NA	NA
RP11-32D16.1	NA	NA	NA	NA
BTN3A2	higher expression associated with improved distant metastasis-free survival in HR-/HER2+ breast cancer	Human tissues	NA	28409241
RP11-73O6.3	NA	NA	NA	NA

AP006621.6	NA	NA	NA	NA
RPLP2	differentially expressed for breast cancer apoptosis (both up- and down-regulation)	*In vitro*	NA	22133146
CTD-3051D23.1	NA	NA	NA	NA
RP11-467J12.4	NA	NA	NA	NA
CTD-3032H12.1	NA	NA	NA	NA
LINC00671	NA	NA	NA	NA
LRRC37A2	NA	NA	NA	NA
LRRC37A	NA	NA	NA	NA
KANSL1-AS1	NA	NA	NA	NA
CRHR1	encodes a receptor of corticotropin-releasing hormone (CRH), which suppresses TGFβ1-induced Epithelial-Mesenchymal Transition in breast cancer cells	*In vitro*	consistent	24412750 26138318
HAPLN4	NA	NA	NA	NA
RP11-15A1.7	NA	NA	NA	NA

NA: not available

Supplementary Table 11. Performance of prediction models and association results for breast cancer target genes reported previously at GWAS-identified loci

Chromosome regions	Target genes	Reference	Evidence from original paper for supporting this gene as the target gene	Performance of expression prediction model (R^2) in GTEx/TCGA	Association of predicted expression with breast cancer risk*
1p33	*NSUN4*	[1]	eQTL analyses in GTEx, TCGA (tumor tissue) and METABRIC (tumor adjacent normal tissue), prediction by ChIA-PET in MCF7 cells	0.01/0.006	$p=1.95 \times 10^{-4}$ (z: negative)
1p36.22	*PEX14*	[2]	eQTL analyses in TCGA (tumor and adjacent normal tissue)	0.02/0	$p=0.002$ (z: positive)
2p23.2	*TRMT61B*	[3]	eQTL analyses in TCGA (tumor tissue) and Norwegian normal breast cohort (normal tissue)	0.23/0.33	$p=0.30$
2q33	*PPIL3*, *CASP8*	[3,4]	eQTL analyses in TCGA (tumor tissue); eQTL analyses in TCGA (tumor adjacent normal tissue) and Westra *et al.* (peripheral blood samples)	0.44/0.59, 0.22/0.30	$p=0.02$ (z: positive), $p=8.51 \times 10^{-16}$ (z: negative)
2q35	*IGFBP5*	[5]	eQTL analyses in the Norwegian Breast Cancer Study and METABRIC (tumor adjacent normal tissue) (marginal significant associations with levels of one of the tested probes, but not any others)	0.04/0.004	NA
4q24	*TET2*	[6]	eQTL analyses in TCGA (tumor tissue) and METABRIC (tumor adjacent normal tissue)	0.007/0.02	$p=0.08$
5p12	*FGF10*, *MRPS30*	[7]	eQTL analyses in GTEx (normal tissue) and Norwegian Breast Cancer Study (tumor and tumor adjacent normal tissue); eQTL analyses in GTEx (normal tissue), and Norwegian Breast Cancer Study and TCGA (both tumor and tumor adjacent normal tissue)	0.02/0, 0.006/0.16	$p=0.26$, $p=1.43 \times 10^{-25}$ (z: positive)
5p15.33	*TERT*	[8]	luciferase reporter assays	NA	NA
5q11.2	*MAP3K1*	[9-11]	Chromosome Conformation Capture and luciferase reporter assays etc, while, no	0.06/0	$p=0.32$

			detectable differences in expression were found across genotypes of the index SNPs		
5q14	*ATP6AP1L*	[12]	eQTL analyses in TCGA (tumor tissue)	0.63/0.32	$p=6.32 \times 10^{-7}$ (z: negative)
6p24.3	*GCNT2*	[13]	eQTL analyses in TCGA (tumor tissue)	NA	NA
6q25	*ESR1*, *RMND1*, *CCDC170*, *AKAP12*	[14,15]	eQTL analyses in TCGA (tumor tissue) and METABRIC (tumor and tumor adjacent normal tissue); eQTL analyses in TCGA (tumor tissue); eQTL analyses in TCGA (tumor tissue) and GTEx (normal tissue); eQTL analyses in TCGA (tumor tissue)	NA, 0.13/0.02, 0.02/NA, NA	NA, $p=1.95 \times 10^{-6}$ (z: positive), $p=0.002$ (z: negative), NA
7q35	*OR2A7*	[10]	eQTL analyses in TCGA (tumor tissue)	0.23/0.12	$p=0.34$
8q24	*POU5F1B*, *PVT1*	[16]	eQTL analyses in TCGA (tumor tissue)	NA, 0.03/0.01	NA, $p=1.12 \times 10^{-4}$(z: positive)
9q31.2	*KLF4*	[11,17]	eQTL analyses in TCGA (tumor tissue)	0.02/0	$p=0.007$ (z: positive)
10q21.2	*NRBF2*	[18]	eQTL analyses in Normal breast I (normal tissue) and Breast carcinomas I (tumor tissue)	NA	NA
10q26.13	*FGFR2*	[19]	prediction by ChIA-PET in MCF7 cells, while no association in eQTL analyses in METABRIC (tumor tissue)	0.13/0.02	$p=0.73$
11p15.5	*TH*	[10]	eQTL analyses in TCGA (tumor tissue)	NA	NA
11q13.1	*AP5B1*	[10]	eQTL analyses in TCGA (tumor tissue)	NA	NA
11q13.3	*CCND1*	[20]	eQTL analyses in the Helsinki Breast Cancer Study (tumor tissue) suggests borderline association for one SNP rs554219 in a recessive model; while there was no linear trend, and no signal detected in analyses of 40 normal breast tissue samples or TCGA tumor samples	NA	NA
15q26.1	*RCCD1*	[21]	eQTL analyses in TCGA (tumor and adjacent normal tissue)	0.13/0.07	$p=3.33 \times 10^{-13}$ (z: negative)
16q12.1	*TOX3*	[10,11]	eQTL analyses in TCGA (tumor tissue)	$0.02/4.27 \times 10^{-5}$	$p=0.09$
16q13	*AMFR*	[1]	eQTL analyses in METABRIC (tumor adjacent normal tissue); prediction by ChIA-PET in MCF7	NA	NA

			cells		
16q23.2	*DYNLRB2*	[10]	eQTL analyses in TCGA (tumor tissue)	NA	NA
17q22	*STXBP4*	[22]	Index SNP associated with differential transcript expression in TCGA (tumor tissue)	0.03/0.01	$p=2.21 \times 10^{-11}$ (z: positive)
19p13	*LRRC25*, *ABHD8*	[10,23,24]	eQTL analyses in TCGA (tumor tissue); eQTL analyses in normal breast tissue	5.36×10^{-6}/0, NA	$p=0.65$, NA
19q13.31	*ZNF404*, *ZNF155*	[2,10]	eQTL analyses in TCGA (tumor tissue); eQTL analyses in TCGA (tumor tissue)	0.15/0.21, 0.13/0.19	$p=1.15 \times 10^{-13}$ (z: positive), $p=0.03$ (z: positive)
21q22.12	*KCNE1*, *RUNX1*, *RCAN1*	[25]	eQTL analyses in TCGA (tumor tissue); eQTL analyses in METABRIC (tumor tissue); eQTL analyses in METABRIC (tumor tissue)	0.08/0.06, 0.04/0, NA	$p=0.65$, $p=0.76$, NA

[*] association analysis of 122,977 cases and 105,974 controls; MetaXcan was used for the association analyses
NA, not applicable

Supplementary Table 13. Primer sequences.

Name	Sequence 5'-> 3'
GUSB Fwd	GAAAATATGTGGTTGGAGAGCTCATT
GUSB Rev	CGAGTGAAGATCCCCTTTTTA
PUM1 Fwd	AATGCAGGCGCGAGAAAT
PUM1 Rev	TTGTGCAGCTGAGGAACTAATGA
RPLP0 Fwd	CCATTGAAATCCTGAGTGATGTG
RPLP0 Rev	CTTCGCTGGCTCCCACTTT
ZSWIM5_H_FWD1	AAGACGGTGGCGGAAAAGTG
ZSWIM5_H_REV1	GAAGGACCAGTAGACGATGCG
ZSWIM5_H_FWD2	AGTCGGCTTTCATCTGAGTGG
ZSWIM5_H_REV2	AGGAAGACGCAATTTGACTTGG
ZSWIM5_H_FWD3	CTATCTCCGAAACCCTTTTCCAG
ZSWIM5_H_REV3	TGTGGTGTGCCGTGATTAAATA
KLHDC10_H_FWD1	CTCAACCGCTTCGTGCAAC
KLHDC10_H_REV1	CCTAACTGGGTCCCATCGTATTT
KLHDC10_H_FWD2	TACGATGGGACCCAGTTAGGA
KLHDC10_H_REV2	TGTGGCCTCTCAAAAACCTGT
KLHDC10_H_FWD3	GCACGAAGTGGACATCGTTG
KLHDC10_H_REV3	CCTCCCGATTCATCATAATCTGG
UBLCP1_H_FWD1	GTGGACAGGAGTATTCAGTGACC
UBLCP1_H_REV1	CAAGTAACTTTTGGCGTTCTGG
UBLCP1_H_FWD2	CTCGCAGAGTGAAAGAGTACAAA
UBLCP1_H_REV2	GCACAAGACCTGTGGTCAAATA
PLEKHD1_H_FWD1	TCCCGGCGGTTTTTCATCATC
PLEKHD1_H_REV1	CCACTGGGTCTGCTCAAACT
PLEKHD1_H_FWD2	GGAAGAGACCGAAGAACTCTGC
PLEKHD1_H_REV2	TGCAAGGACTCCGTGAGGT
ALS2CR12_H_FWD1	ACTTGGGACCACGGAAGCTA
ALS2CR12_H_REV1	GGAGCTGGTACAAGAGGAGTTA
ALS2CR12_H_FWD2	ATGCACAAGCCCTTATCCTAGA
ALS2CR12_H_REV2	AGAGGCCAATCTCCCAGAACA

RMND1_H_FWD1	CAGTGCCGAAGAATCGGTCAT
RMND1_H_REV1	CGAGCAGCATTTAATGGAGACA
RMND1_H_FWD2	GCACACCTTCCAACCATGAAA
RMND1_H_REV2	TGGATGCTTTTAGTGGTCTCTTC
RMND1_H_FWD3	GAGACCACTAAAAGCATCCAGG
RMND1_H_REV3	GCAGTGCATTAGGTCCTCGT
STXBP4_H_FWD1	CCTTGGCCTGAAGGTACTAGG
STXBP4_H_REV1	AGCAGATTCTAACCTCAACTTGG
STXBP4_H_FWD2	GAATCTGCTTGGGAGATAGCATT
STXBP4_H_REV2	TGAGGCTTGAGGTCCATATTCT
STXBP4_H_FWD3	ATCCCTCTGTTCGCTTTAAGGC
STXBP4_H_REV3	TCAGGGCTTGGTGTTGTTCC
ZNF404_H_FWD1	AAGTAAATGCGTACCATCAGGAG
ZNF404_H_REV1	TCCCACTTTAGGTCTCTGTTGT
ZNF404_H_FWD2	GGCCTTTGTTCGCAGCTATCT
ZNF404_H_REV2	AGGCTTGAGCCCTTACCAAAA
ZNF404_H_FWD3	GGCCTTTTGTAGAGGCTCTCA
ZNF404_H_REV3	AAGGTCTCCAACACGACTGAA
PIDD1_H_FWD1	TCAGAGGATTCGGACGCAG
PIDD1_H_REV1	GTGAGTGCTCAGACGCAAGAA
PIDD1_H_FWD2	GAGCCTCGTCGAGTCTCCAT
PIDD1_H_REV2	GGCCCAGTACAACAGGTGC
PIDD1_H_FWD3	CTCACCCACCTGTACGCAC
PIDD1_H_REV3	CAGAGCGATGAGGTTCACAC
NRBF2_H_FWD1	CAGACGAGCAGACCGTTTATT
NRBF2_H_REV1	TGCTGGGCTTTCAATCTTTCTT
ABHD8_H_FWD1	GGGGTGACCGACGGTATCT
ABHD8_H_REV1	GGCTTGACCTCTACAAAGGTG
ABHD8_H_FWD2	TCGAGCCGACCTCCTACAC
ABHD8_H_REV2	TTTGCAGCTAGTGATGCGCTT
ABHD8_H_FWD3	CTGAGGACATGCGAGCAATCT
ABHD8_H_REV3	GAAAGAGACACCGTAGGAATGG

RP11-218M22.1_H_R1_FWD1	CGGGAAAAGATGGAGTGAAGGT
RP11-218M22.1_H_R1_REV1	GGCACTTCCGCTAATGCTG
RP11-218M22.1_H_R1_FWD2	TGAGCCGGGAAAAGATGGAGT
RP11-218M22.1_H_R1_REV2	GCACTTCCGCTAATGCTGAGG
RP11-218M22.1_H_R2_FWD1	CACTGAGAGAAGCAGGAGAATGT
RP11-218M22.1_H_R2_REV1	AAGAGAGATTGTCTCGCAGTC
RP11-218M22.1_H_R2_FWD2	ACTGAGAGAAGCAGGAGAATGT
RP11-218M22.1_H_R2_REV2	AAAGAGAGATTGTCTCGCAGTC
AP006621.6_H_FWD1	TCCTGAGGGCCGACTCTAC
AP006621.6_H_REV1	CGTCTTAGCGGCTGTCACTT
AP006621.6_H_FWD2	ACTGAGAGAAGCAGGAGAATGTT
AP006621.6_H_REV2	CACTAAAGAGAGATTGTCTCGCA
RP11-467J12.4_H_FWD1	GGGGTGGTGGGTGTCACTAA
RP11-467J12.4_H_REV1	ATTCACCTTCACCAGGGCAC
RP11-467J12.4_H_FWD2	TCACTAAAAGGAACCAGCCCC
RP11-467J12.4_H_REV2	CTCTGACTGATTCACCTTCACCA
RP11-15A1.7_H_FWD1	CAGAGTGTGTCTGGACTCCG
RP11-15A1.7_H_REV1	CCAGGCGCTCAGAGATATGG
RP11-15A1.7_H_FWD2	GCGACTCAGAGTGTGTCTGG
RP11-15A1.7_H_REV2	ATGGAATACGTTCCCGGTGG
CTD-3032H12.1_H_FWD1	CCTACACGAGGCCAGAGATCC
CTD-3032H12.1_H_REV1	CCTAACAGCAGATCGCCTCG
CTD-3032H12.1_H_FWD2	GCCCGTGGCCTACACGAG
CTD-3032H12.1_H_REV2	CGGGTCTTCCTTTGTGTCCAG
B2M-FWD-1	GAGGCTATCCAGCGTACTCCA
B2M-REV-1	CGGCAGGCATACTCATCTTTT
B2M-FWD-2	CTCACGTCATCCAGCAGAGA
B2M-REV-2	CGGCAGGCATACTCATCTTT
B2M-FWD-3	AGGCTATCCAGCGTACTCCA
B2M-REV-3	CGGCAGGCATACTCATCTTT
ARHGDIA-FWD-1	GGATGAGCACTCGGTCAACTA
ARHGDIA-REV-1	GGCCTCCTTGTACTTTCGCAG

ARHGDIA-FWD-2	GAGCCTGCGAAAGTACAAGG
ARHGDIA-REV-2	TCCTTCAGCACAAACGACTG
ARHGDIA-FWD-2	TGCCTCTGCCTTTTCTGTCT
ARHGDIA-REV-3	GCACTTGGTCCCTTGTTTGT
ZAP70-FWD-1	CGAGCGTGTATGAGAGCCC
ZAP70-REV-1	ATGAGGAGGTTATCGCGCTTC
ZAP70-FWD-2	ACGCCAAGATCAGCGACTTT
ZAP70-REV-2	GGGTGCGTACCACTTGAGC
ZAP70-FWD-3	CTGGAGCTATGGGGTCACCA
ZAP70-REV-3	CAGGCTGTAGTAACAGGCTCG

Supplementary Note

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Supplementary Excel Table guide

Supplied in a combined file

Supplementary Table 2
Genes with predicted expression levels associated with breast cancer risk at $p<1.05 \times 10^{-3}$ (the significance level with false discovery rate correction)

Supplementary Table 3
Associations of predicted expression of identified genes with breast cancer risk in each of the three assessed datasets (OncoArray, iCOGS, and GWAS sets)

Supplementary Table 4
Full list of all risk SNPs within the same genomic loci/region of the identified associated genes in Tables 1-4 and their distances with the associated genes

Supplementary Table 7
Canonical pathways, diseases and bio functions, and networks associated with identified breast cancer associated genes, and highly co-expressed protein-coding genes of the identified novel susceptibility long non-coding RNAs

Supplementary Table 12
Predicting variants in gene expression prediction models for the identified associated genes after Bonferroni correction