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Common susceptibility loci for male breast cancer

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Abstract

Background: The aetiology of male breast cancer (MBC) is poorly understood. In particular, the extent to which the genetic basis of MBC differs from female breast cancer (FBC) is unknown. A previous genome-wide association study (GWAS) of MBC identified two predisposition loci for the disease, both of which were also associated with risk of FBC.

Methods: We performed genome-wide single nucleotide polymorphism (SNP) genotyping of European ancestry MBC case subjects and controls, in three stages. Associations between directly genotyped and imputed SNPs with MBC were assessed using fixed-effects meta-analysis of 1,380 cases and 3,620 controls. Replication genotyping of 810 cases and 1,026 controls was used to validate variants with *P*-values < 1×10^{-06}. Genetic correlation with FBC was evaluated using LD score regression, by comprehensively examining the associations of published FBC risk loci with risk of MBC and by assessing associations between a FBC polygenic risk score (PRS) and MBC. All statistical tests were two-sided.

Results: The GWAS identified three novel MBC susceptibility loci that attained genome-wide significance ($P < 5 \times 10^{-08}$). Genetic correlation analysis revealed a strong shared genetic basis with estrogen-receptor (ER) positive FBC. Males in the top quintile of genetic risk had a four-fold increased risk of breast cancer relative to those in the bottom quintile (odds ratio = 3.86, 95% confidence interval = 3.07 to 4.87, $P = 2.08 \times 10^{-30}$).

Conclusions: These findings advance our understanding of the genetic basis of MBC, providing support for an overlapping genetic aetiology with FBC and identifying a four-fold high risk group of susceptible men.

Male breast cancer (MBC) is rare, accounting for fewer than 1% of all breast cancer diagnoses. A greater proportion of male than female breast cancers (FBC) are of the estrogen-receptor (ER) positive subtype (>95% MBC vs. 75% FBC) suggesting that MBC may comprise a more homogeneous group of tumours than FBC. Although there is a paucity of data regarding the aetiology of MBC, family history and genetic susceptibility are important risk factors (1, 2). Approximately 10% of cases are attributable to inherited mutations in *BRCA2* (1). Conversely, mutations in *BRCA1* are observed in only a small number of cases suggesting differences in the underlying genetic aetiologies of MBC and FBC (1).

Common germline variants influence susceptibility to MBC (3-5). Our previous genome-wide association study (GWAS) of MBC identified single nucleotide polymorphisms (SNPs) at 14q24.1 and 16q12.1 that were associated with susceptibility at genome-wide levels of significance (4). Moreover, although these loci were also associated with FBC susceptibility (6, 7), they conferred greater risks of breast cancer in men than women (14q24.1 odds ratio [OR] = 1.57 vs 1.07 and 16q12.1 OR = 1.50 vs 1.22 for MBC and FBC respectively) (4), lending weight to findings from population-based family-history studies which suggest a greater contribution of genetic variation to MBC than FBC predisposition (2).

In this study we have pooled individual-level data from our GWAS (4) with two additional case-control datasets to identify novel MBC risk variants, to illuminate better the genetic basis of MBC and to enable comparisons between determinants of polygenic predisposition to MBC and FBC.

Methods

Subjects

Cases for discovery analysis were primarily from the Breast Cancer Now Male Breast Cancer Study, a population-based case-control study of MBC in England and Wales (UK-BCN-MBCS, n = 1,210). Additional cases were from UK studies at the University of Leeds (UK-UoL, n = 31) and the University of Cambridge (UK-UoC, n = 138), and a US study at City of Hope (US-CoH, n = 113). The UK-UoL, UK-UoC, US-CoH and 540 of the UK-BCN-MBCS cases have been analysed previously (4). Here we have added an additional 670 MBC cases from the UK-BCN-MBCS. To estimate autosomal SNP genotype frequencies from the general population, we used male and female controls from the 1958 British Birth Cohort (UK-58BC, n = 2,663), male controls from the UK-BCN-MBCS (n = 264) and female controls from the UK Generations Study (UK-GS, n = 698) (**Supplementary Table 1**) (8). The inclusion of female controls was predicated upon the observation that autosomal SNPs do not differ in frequency between males and females sampled from the same ancestral population so that GWAS of sexually differentiated traits, such as breast cancer, need not be restricted to selection of same sex controls (9). Descriptions of each of the studies that were used for discovery analysis are provided in **Supplementary Methods**. For validation of promising associations, we used 810 cases and 1,026 controls of European ancestry that were assembled internationally for our previous GWAS (**Supplementary Table 1**) (4). All sample collection was undertaken with informed consent and ethical approval.

Genotyping, Quality Control and Imputation

Discovery analysis samples, genotyping arrays and SNPs / samples excluded during quality control are summarised in **Supplementary Figure 1**. Genotyping was performed using Illumina (San Diego, CA) Infinium OmniExpress 710K BeadChips (OE; UK-BCN-MBCS, UK-UoL, UK-UoC and US-CoH cases), Infinium OncoArray 500K BeadChips (OA; UK-BCN-MBCS cases and UK-GS controls) and Infinium Global Screening Array 640K BeadChips (GSA; UK-BCN-MBCS cases and controls). UK-58BC controls were genotyped using Infinium 1.2M BeadChips. Replication genotyping was performed using either Agena (San Diego, CA) iPLEX chemistry or with KASP assays (LGC, Hoddesdon, UK).

Samples were excluded based upon genotyping completion rate (< 95.0%), relatedness (IBD first- and second-degree relatives) and genetically determined non-European ancestry. SNPs were excluded according to call rates (< 95.0%), MAF (< 2.0%) and genotype deviation from Hardy-Weinberg proportions ($P < 1 \times 10^{-05}$). SNP data from cases genotyped using OE BeadChips was harmonised with UK-58BC control data yielding 486,160 SNPs. Cases and controls genotyped using OA were similarly harmonised, as were those using GSA. Genome-wide imputation was performed for each GWAS dataset using 1KGP Phase 3 reference data. Haplotypes were pre-phased using SHAPEIT2 (10) and imputation was performed using IMPUTE2 (11). Imputed SNPs with INFO scores < 0.80 and / or MAFs < 2.0% were excluded. After QC, 8,074,073 SNPs were available for analysis.

Statistical Analysis

For each GWAS dataset, tests of association between imputed SNPs and MBC status were performed, assuming a log-additive model, using SNPTEST v2.5

(12). Quantile–quantile plots showed no evidence of over-dispersion (λ = 0.99 to 1.05, **Supplementary Figure 2**). Combined analysis of each dataset was performed using fixed-effects inverse variance-weighted meta-analysis (**Supplementary Figure 3**) (13). Heterogeneity was assessed using Cochran's Q-test and I^2 statistics. Sensitivity analyses of the effect estimates when US-CoH cases or UK-GS and UK-58BC female controls were omitted were consistent with the main results (**Supplementary Tables 2 and 3**). For replication analysis, effects under a log-additive model were estimated by performing multiple logistic regression, adjusted for study, using the Genotype Libraries and Utilities package (14). Bayesian false discovery probabilities (BDFP) were calculated to assess the noteworthiness of FBC predisposition SNP associations with MBC assuming that the cost of a false non-discovery was four times that of a false discovery (giving a noteworthiness cut-off value of 0.80) and that the OR lies between 0.83 and 1.2 with probability 0.95 (15). These comparisons were restricted to 172 published loci with FBC $P < 5 \times 10^{-08}$ (16). To compare the MBC ORs with those of FBC, we assumed both sets of ORs were log-normally distributed and that the difference between the log ORs was normally distributed with mean zero and variance equal to the sum of the squared standard errors of the two estimates to obtain a χ^2 statistic. All statistical tests were two-sided and $P < .05$ was used as the cut point for statistical significance unless otherwise stated.

Heritability and Genetic Correlation

The heritability of MBC, h_g^2, was estimated assuming a continuous underlying liability and an MBC population prevalence of 0.1%, using LD score regression (LDSC) (17). LDSC was used to calculate the genetic correlation, r_g, between MBC

and FBC using summary statistics from 122,977 FBC cases and 105,974 controls in the Breast Cancer Association Consortium (BCAC) (16). Subtype specific genetic correlations between MBC and both ER-positive and ER-negative FBC also used BCAC data (n = 69,501 ER-positive and n = 21,468 ER-negative cases). To assess cross-cancer genetic correlations with other hormonally driven cancers we used summary statistics from 79,148 prostate cancer cases and 61,106 controls in the PRACTICAL consortium (18) and 22,406 invasive epithelial ovarian cancer cases and 40,941 controls in the OCAC consortium (19).

Polygenic Risk Score Analysis

A 313-SNP FBC polygenic risk score (PRS) (20) was calculated using effect estimates for overall, ER-positive and ER-negative FBC, standardised such that the PRS distribution in controls (2,663 male and female individuals from the UK-58BC) had mean = 0 and standard deviation = 1. The 313-SNP FBC PRS includes 305 SNPs that were associated with overall FBC at $P < 1 \times 10^{-05}$ plus six additional SNPs that were associated with ER-positive FBC and two rare variants in the *BRCA2* and *CHEK2* genes (20). To enable comparison with FBC, we derived PRS for 1,671 female cases from UK-GS (9). Logistic regression was used to estimate risk of MBC by quintiles and per standard deviation increase in the PRS.

Gene Expression and eQTL Analysis

Expression quantitative trait locus (eQTL) analyses were performed using GTEx gene expression data on normal breast samples from 157 males and 107 females (21). Associations between $\log_{10}$ normalised gene-counts of candidate target-genes and SNP genotypes were assessed using linear regression, with and

without interaction terms for genotype and sex. Linear regression was used to assess associations between gene-expression of putative target-genes and sex.

Results

Heritability of MBC and Genetic Correlation With FBC

After quality control, the three GWAS datasets yielded SNP genotypes at 8,074,073 loci in 1,380 MBC cases and 3,620 controls. The heritability of MBC attributable to common SNPs, h_g^2, was 0.09 (SE = 0.06) on the liability scale, which is accordant with published estimates for FBC (22). Using cross-trait LDSC, we observed strong genetic correlation, r_g, between MBC and FBC (r_g= 0.83, SE = 0.30, *P* =.005). Consistent with the predominance of ER-positive tumours in MBC, genetic correlation was stronger between MBC and ER-positive FBC (r_g= 0.82, SE = 0.30, *P* = .005), than ER-negative FBC (r_g= 0.47, SE = 0.24, *P* = .047). Predicated on evidence of pleiotropy between breast cancer and other hormonally driven epithelial tumours (23), we estimated genetic correlation between MBC and both prostate and ovarian cancer. While there was no evidence of genetic correlation with prostate cancer (r_g= 0.01, SE = 0.11, *P* = .90) there was borderline evidence of a moderate genetic correlation with ovarian cancer (r_g= 0.55, SE = 0.29, *P* = .06).

GWAS and Validation Analysis

Combined analysis of the GWAS datasets detected a novel genome-wide statistically significant association ($P < 5 \times 10^{-08}$) between SNP rs9371545 at 6q25.1 and risk of MBC ($P = 1.63 \times 10^{-08}$, **Table 1**, **Supplementary Table 4**) and validated the associations at 14q24.1 (rs1022979 $P = 1.53 \times 10^{-16}$) and 16q12.1 (rs35850695 $P = 1.57 \times 10^{-11}$, **Supplementary Table 4**). We observed promising associations (*P*

< 1 x 10^{-06}) at 11q13.3 (rs78540526 and rs554219, **Table 1**, **Supplementary Table 4**) and 15q24 (rs4407020, **Supplementary Table 4**). Replication genotyping of 810 cases and 1,026 controls provided support for rs78540526 and rs554219 (**Table 1**, **Supplementary Table 4, Supplementary Figure 4**), but not rs4407020 (**Supplementary Table 4**) in a joint analysis with the discovery data (rs78540526 *P* = 1.06 x 10^{-11}, rs554219 *P* = 2.86 x 10^{-11}). Similar to the loci at 14q24.1 and 16q12.1, the 6q25.1 and 11q13.1 SNPs are also associated with predisposition to FBC but have larger risk effects in males (**Table 1**).

Associations Between FBC Predisposition SNPs and Risk of MBC

We next evaluated the MBC associations of 172 published FBC risk SNPs (16) (**Supplementary Table 5**). Thirty-five SNPs (20.3%) had *P* < .05 and consistent directions of effect with FBC; 33 remained noteworthy using BFDP analysis (15). Eight loci had statistically significant differences in their ORs for MBC and FBC (FDR < 0.10, **Table 2**, **Supplementary Table 6**). At 6q25.1 and 14q24.1, rs9397437 and rs2588809 had ORs that were greater for MBC than FBC, while rs2981578 at 10q26.13 had an OR that was greater for FBC. The directions of the ORs for rs4233486 at 1p34.2, rs12710696 at 2p24.1, rs13066793 at 3p12.1, rs3215401 at 5p15.33 and rs10816625 at 9q31.2 were opposite to FBC.

At each of the 172 loci we investigated whether any variants correlated ($r^2 \geq 0.10$) with a published FBC susceptibility SNP were more statistically significantly associated with MBC in our GWAS than the FBC SNP itself (**Supplementary Table 5)**. We identified four such SNPs with *P* < 1 x 10^{-05}, at 6q25.1, 10p12.31 and 11q13.3, which we genotyped alongside the corresponding lead FBC predisposition SNPs in our replication samples and analysed jointly with the discovery data (**Figure**

1, **Table 3, Supplementary Table 5**). At 6q25.1, rs9383938 (P = 2.93 x 10^{-09}) was correlated with FBC SNP rs9397437 (P = 5.29 x 10^{-09}, r^2 = 0.83) but was nominally more statistically significantly associated with MBC. SNP rs146723925 was correlated (r^2 = 0.89) with a second FBC risk locus at 6q25.1 demarcated by rs3757322 and was more statistically significantly associated with MBC in the discovery data, but failed assay design for replication genotyping. However, rs3757322 surpassed the genome-wide significance threshold following joint analysis (P = 6.23 x 10^{-09}) and conditional analyses indicated that rs3757322 and rs9383938 tag independent causal alleles at 6q25.1 (**Supplementary Table 7**). At 10p12.31, rs2183271 (P = 2.69 x 10^{-07}) was several orders of magnitude more strongly associated with MBC than lead FBC SNP rs7072776 (P = 2.46 x 10^{-04}, r^2 = 0.68) and the effect of rs7072776 was strongly dependent upon rs2183271 (**Figure 1, Table 3, Supplementary Tables 5 and 7**). At 11q13.3, rs78540526 (P = 1.06 x 10^{-11}) was correlated with FBC SNP rs75915166 (P = 7.71 x 10^{-08}, r^2 = 0.63, **Figure 1, Table 3, Supplementary Table 5**). rs75915166 and a second variant at 11q13.3, rs554219, have been reported to independently influence risk of FBC (24). Analysis of these SNPs conditioned on rs78540526 did not provide compelling evidence for independence in MBC (P-values = .64 and .03 respectively). However, rs554219 (P = 4.74 x 10^{-05}; **Supplementary Table 7**), and rs78540526 (P = 5.55 x 10^{-05}) were associated with MBC after conditioning on rs75915166.

FBC PRS Association With MBC

Since our data supported a strong genetic correlation between MBC and FBC, we assessed whether a recent 313-SNP FBC PRS (20) was associated with breast cancer risk in our study. The OR per standard deviation increase in the PRS was

1.55, 95% confidence interval (CI) = 1.45 to 1.66, $P = 3.54 \times 10^{-37}$ (**Table 4**). Men in the top quintile of genetic risk had an almost four-fold increased risk of breast cancer (OR = 3.86, 95% CI = 3.07 to 4.87, $P = 2.08 \times 10^{-30}$) compared with men in the bottom quintile. We examined MBC associations with the 313-SNP PRS incorporating weightings for ER-positive or ER-negative FBC. Risk estimates for the ER-positive PRS were similar to the overall PRS; the ER-negative PRS was less strongly associated with MBC risk (**Table 4**), consistent with our genetic correlation analysis. The PRS distribution in male cases was similar to that of FBC cases (**Figure 2**).

Candidate Target-gene Expression in Male and Female Breast Tissue

Functional studies have identified putative target-genes for five of the eight FBC predisposition loci that had statistically significant differences in their ORs for FBC and MBC: *TERT* at 5p15.33, *ESR1* and *CCDC170* at 6q25.1, *KLF4* at 9q31.2, *FGFR2* at 10q26.13 and *ZFP36L1* at 14q24.1 (25-30). By examining GTEx multi-tissue expression quantitative trait locus (eQTL) analyses (31) we suggest that *CITED4* (rs4233486 $P = 2.36 \times 10^{-11}$) and *VGLL3* (rs13066793 $P = 1.21 \times 10^{-07}$) are candidate target-genes at the loci mapping to 1p34.2 and 3p12.1 (21). *CITED4* encodes Cbp/p300-interacting transactivator 4, a transcriptional coactivator that is induced during lactogenic differentiation of breast epithelial cells and is involved in milk secretion (32) while *VGLL3* encodes transcription cofactor vestigial-like protein 3 and may act as a tumour suppressor gene in high-grade serous ovarian carcinoma (33).

We hypothesised that variation in the basal gene expression levels of predisposition SNP target-genes in male and female breast tissue might partly

explain the different MBC and FBC risks observed at these loci. To investigate, we evaluated GTEx RNA-seq data from 157 males and 107 females. Four candidate target-genes had statistically significant sex-biased tissue expression (**Supplementary Figure 5**). *CITED4* at 1p34.2 (P = 3.00 x 10^{-25}) and *FGFR2* at 10q26.13 (P = 3.24 x 10^{-10}) had higher expression in female than male breast tissue, while *KLF4* at 9q31.2 (P = 9.10 x 10^{-10}) and *CCD170* at 6q25.1 (P = 2.80 x 10^{-04}) were more highly expressed in males than females.

We also assessed eQTL associations between the lead SNPs at these loci and their candidate target-genes using GTEx data from breast tissue (n = 264). The risk allele of rs13066793 at 3p12.1 was associated with reduced expression of *VGLL3* (P = .02, **Supplementary Figure 6**), albeit the association was not statistically significant after adjusting for multiple comparisons. SNP rs3757322 at 6q25.1 was borderline associated with expression of *CCDC170* (P = .06) and this association varied according to sex (P = .02, **Supplementary Figure 7**). There was no evidence of breast-specific eQTL associations with target-genes at the other loci, which could reflect limited power to detect subtle differences in gene expression.

Discussion

We have performed the largest genetic association study of MBC to date by conducting, as is usual in GWAS, genome-wide imputation and meta-analysis of existing (4) and newly generated genotyping data. We identified three novel MBC predisposition loci that attained genome-wide levels of significance, of which two mapped to 6q25.1 and one mapped to 11q13.3, bringing the total number of confirmed predisposition loci to five. Notably, each of these loci is also associated

with risk of FBC and almost 20% of confirmed FBC susceptibility SNPs showed evidence of association with MBC predisposition. To date, no low penetrance alleles have been identified that are exclusively associated with MBC but not FBC. Although our study does not rule out the possibility that such loci exist, it does suggest that the magnitudes of their effects will be small. While differences between the frequencies of pathogenic *BRCA1* and *BRCA2* mutations have led to the suggestion that MBC and FBC have distinct genetic aetiologies, our genetic correlation analysis provides evidence of a shared genetic basis for MBC and ER-positive FBC. Interestingly, we detected borderline evidence (P = .06) of a cross-cancer genetic correlation between MBC and ovarian cancer, consistent with a recently reported genetic correlation between FBC and ovarian cancer (22).

Lecarpentier *et al* recently demonstrated that a FBC PRS is associated with breast cancer risk in male *BRCA1/2* mutation carriers (34). We show here, for the first time, that a FBC PRS is associated with MBC risk in men from the general population. The OR per standard deviation increase in the PRS for males is almost identical to that of unselected females and is greater than that of male *BRCA1/2* mutation carriers (20, 34, 35). While risk stratification amongst the general population using a PRS is unfeasible given both the rarity of MBC and level of risk differentiation, the striking similarity between the PRS distributions of MBC and FBC cases suggests that a larger number of FBC predisposition variants than were detected by our study probably influence susceptibility to MBC.

Although our genetic correlation analysis indicated that MBC shares a pronounced genetic basis with ER-positive FBC, there are distinctions. For example, we observed several MBC associations amongst SNPs that confer greater risks of ER-negative than ER-positive FBC, including SNP rs9371545 at 6q25.1 and the

BRCA2 truncating variant rs11571833. Conversely, several SNPs that are most strongly associated with ER-positive FBC were not associated with MBC including rs11249433 at 1p11.2, rs34005590 at 2q35 and rs2981578 at 10q26.13. Whilst this may be a consequence of power, the ER-positive FBC OR for rs2981578 is large and should be detectable in our study. We hypothesise that the underlying aetiological mechanisms affected by SNPs that had statistically significant differences in their ORs for MBC and FBC might be influenced by sex-specific differences in expression or activity of their target-genes, or by different endogenous factors in males and females. The comparatively lower expression of *FGFR2* in male than female breast tissue, as observed in GTEx data, could explain the lack of an MBC association with rs2981578 at the 10q26.13 locus, despite it being amongst the most strongly associated SNPs with ER-positive FBC.

The principal limitation of our study was its relatively small size compared to typical cancer GWAS. Consequently, it had limited capacity to detect MBC predisposition loci that are associated with small risk effects and much larger studies will be needed for their discovery. The merits, or otherwise, of continually striving to identify polygenic determinants of disease susceptibility that confer relatively small effects have been debated extensively, particularly since they may have limited clinical usefulness in the short-term. However, all statistically robust genetic associations (even those with small effects) are underpinned by risk alleles that perturb biological processes, of which some might harbour effective targets for therapeutic intervention (36), thus justifying efforts that could lead to their detection. The subsequent illumination of the target-genes and pathways that underlie risk associations in MBC will also likely be difficult, not least because of a paucity of cell-line models derived from male breast tumours for functional analysis. In conclusion,

our findings indicate several elements of shared genetic basis for susceptibility to MBC and FBC, provide further support for a polygenic component to MBC susceptibility and advance our understanding of the genetics of MBC development.

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References

1. Basham VM, Lipscombe JM, Ward JM*, et al.* BRCA1 and BRCA2 mutations in a population-based study of male breast cancer. Breast Cancer Res 2002;4(1):R2.

2. Bevier M, Sundquist K, Hemminki K. Risk of breast cancer in families of multiple affected women and men. Breast Cancer Res Treat 2012;132(2):723-8.

3. Orr N, Cooke R, Jones M*, et al.* Genetic variants at chromosomes 2q35, 5p12, 6q25.1, 10q26.13, and 16q12.1 influence the risk of breast cancer in men. PLoS Genet 2011;7(9):e1002290.

4. Orr N, Lemnrau A, Cooke R*, et al.* Genome-wide association study identifies a common variant in RAD51B associated with male breast cancer risk. Nat Genet 2012;44(11):1182-4.

5. Silvestri V, Rizzolo P, Scarno M*, et al.* Novel and known genetic variants for male breast cancer risk at 8q24.21, 9p21.3, 11q13.3 and 14q24.1: results from a multicenter study in Italy. Eur J Cancer 2015;51(16):2289-95.

6. Easton DF, Pooley KA, Dunning AM*, et al.* Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007;447(7148):1087-93.

7. Thomas G, Jacobs KB, Kraft P*, et al.* A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). Nat Genet 2009;41(5):579-84.

8. Swerdlow AJ, Jones ME, Schoemaker MJ*, et al.* The Breakthrough Generations Study: design of a long-term UK cohort study to investigate breast cancer aetiology. Br J Cancer 2011;105(7):911-7.

9. Boraska V, Jeroncic A, Colonna V*, et al.* Genome-wide meta-analysis of common variant differences between men and women. Hum Mol Genet 2012;21(21):4805-15.

10. Delaneau O, Zagury JF, Marchini J. Improved whole-chromosome phasing for disease and population genetic studies. Nat Methods 2013;10(1):5-6.

11. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genet 2009;5(6):e1000529.

12. Marchini J, Howie B, Myers S*, et al.* A new multipoint method for genome-wide association studies by imputation of genotypes. Nat Genet 2007;39(7):906-13.

13. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 2010;26(17):2190-1.

14. Yeager M, Orr N, Hayes RB*, et al.* Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet 2007;39(5):645-9.

15. Wakefield J. A Bayesian measure of the probability of false discovery in genetic epidemiology studies. Am J Hum Genet 2007;81(2):208-27.

16. Michailidou K, Lindstrom S, Dennis J*, et al.* Association analysis identifies 65 new breast cancer risk loci. Nature 2017;551(7678):92-94.

17. Bulik-Sullivan B, Finucane HK, Anttila V*, et al.* An atlas of genetic correlations across human diseases and traits. Nat Genet 2015;47(11):1236-41.

18. Schumacher FR, Al Olama AA, Berndt SI*, et al.* Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. Nat Genet 2018;50(7):928-936.

19. Phelan CM, Kuchenbaecker KB, Tyrer JP*, et al.* Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet 2017; 10.1038/ng.3826.

20. Mavaddat N, Michailidou K, Dennis J*, et al.* Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. Am J Hum Genet 2019;104(1):21-34.

21. GTEx Consortium. The Genotype-Tissue Expression (GTEx) project. Nat Genet 2013;45(6):580-5.

22. Jiang X, Finucane HK, Schumacher FR*, et al.* Shared heritability and functional enrichment across six solid cancers. Nat Commun 2019;10(1):431.

23. Kar SP, Beesley J, Amin Al Olama A*, et al.* Genome-Wide Meta-Analyses of Breast, Ovarian, and Prostate Cancer Association Studies Identify Multiple New Susceptibility Loci Shared by at Least Two Cancer Types. Cancer Discov 2016;6(9):1052-67.

24. French JD, Ghoussaini M, Edwards SL*, et al.* Functional variants at the 11q13 risk locus for breast cancer regulate cyclin D1 expression through long-range enhancers. Am J Hum Genet 2013;92(4):489-503.

25. Baxter JS, Leavy OC, Dryden NH*, et al.* Capture Hi-C identifies putative target genes at 33 breast cancer risk loci. Nat Commun 2018;9(1):1028.

26. Bojesen SE, Pooley KA, Johnatty SE*, et al.* Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. Nat Genet 2013;45(4):371-84, 384e1-2.

27. Dunning AM, Michailidou K, Kuchenbaecker KB*, et al.* Breast cancer risk variants at 6q25 display different phenotype associations and regulate ESR1, RMND1 and CCDC170. Nat Genet 2016;48(4):374-86.

28. Li Q, Seo JH, Stranger B*, et al.* Integrative eQTL-based analyses reveal the biology of breast cancer risk loci. Cell 2013;152(3):633-41.

29. Meyer KB, O'Reilly M, Michailidou K*, et al.* Fine-scale mapping of the FGFR2 breast cancer risk locus: putative functional variants differentially bind FOXA1 and E2F1. Am J Hum Genet 2013;93(6):1046-60.

30. Orr N, Dudbridge F, Dryden N*, et al.* Fine-mapping identifies two additional breast cancer susceptibility loci at 9q31.2. Hum Mol Genet 2015;24(10):2966-84.

31. Sul JH, Han B, Ye C*, et al.* Effectively identifying eQTLs from multiple tissues by combining mixed model and meta-analytic approaches. PLoS Genet 2013;9(6):e1003491.

32. Sornapudi TR, Nayak R, Guthikonda PK*, et al.* Comprehensive profiling of transcriptional networks specific for lactogenic differentiation of HC11 mammary epithelial stem-like cells. Sci Rep 2018;8(1):11777.

33. Gambaro K, Quinn MC, Wojnarowicz PM*, et al.* VGLL3 expression is associated with a tumor suppressor phenotype in epithelial ovarian cancer. Mol Oncol 2013;7(3):513-30.

34. Lecarpentier J, Silvestri V, Kuchenbaecker KB*, et al.* Prediction of Breast and Prostate Cancer Risks in Male BRCA1 and BRCA2 Mutation Carriers Using Polygenic Risk Scores. J Clin Oncol 2017;35(20):2240-2250.

35. Mavaddat N, Pharoah PD, Michailidou K*, et al.* Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst 2015;107(5).

36. Price AL, Spencer CC, Donnelly P. Progress and promise in understanding the genetic basis of common diseases. Proc Biol Sci 2015;282(1821):20151684.

Table 1. Three novel risk variants with $P < 5 \times 10^{-08}$ identified from analysis of GWAS and replication data and their ORs for FBC.

Cytoband	SNP	Alleles[b]	Stage	Control MAF	Case MAF	MBC OR (95% CI)	*P*-value[c]	FBC OR (95% CI)[d]	*P*-het[e]	I^2
6q25.1	rs9371545[a]	G/A	GWAS	0.07	0.10	1.60 (1.36-1.89)	1.63×10^{-08}	-	-	-
	rs9383938[a]	G/T	Replication	0.09	0.11	1.30 (1.04-1.63)	.02	-	-	-
			Joint	-	-	1.47 (1.30-1.67)	2.93×10^{-09}	1.11 (1.08-1.14)	9.56×10^{-06}	94.9
11q13.3	rs554219	C/G	GWAS	0.12	0.16	1.42 (1.24-1.62)	1.86×10^{-07}	-	-	-
			Replication	0.11	0.16	1.52 (1.25-1.84)	2.65×10^{-05}	-	-	-
			Joint	-	-	1.45 (1.31-1.62)	2.86×10^{-11}	1.27 (1.24-1.31)	.02	82.9
11q13.3	rs78540526	C/T	GWAS	0.07	0.10	1.58 (1.34-1.87)	7.38×10^{-08}	-	-	-
			Replication	0.06	0.10	1.68 (1.32-2.14)	2.45×10^{-05}	-	-	-
			Joint	-	-	1.61 (1.40-1.85)	1.06×10^{-11}	1.39 (1.35-1.42)	.04	76.2

[a] SNP rs9383938 is a proxy for rs9371545 ($r^2 = 0.90$) which failed assay design for replication genotyping. Summary statistics for replication and joint analysis are based on rs9383938.

[b] Alleles are shown as major/minor allele based on control frequencies.

[c] MBC *P*-values were derived from fixed-effects inverse variance-weighted meta-analysis (GWAS and Joint) and from multiple logistic regression, adjusted for study (Replication). All tests were two-sided.

[d] ORs for ER-positive FBC from (16).

[e] *P*-value for Cochran's Q-test for heterogeneity between the MBC and FBC ORs.

[-] Control and case MAFs were not calculated for meta-analysed SNPs at the joint analysis stage. FBC OR, *P*-het and I^2 are not applicable for GWAS and replication stages since published FBC ORs were compared only to the MBC ORs estimated in joint analysis of our GWAS and replication studies.

Table 2. FBC predisposition SNPs with FDR adjusted *P* < .10 that confer statistically significantly different risk effects in males and females.

Cytoband	SNP	Alleles[a]	MBC OR (95% CI)	FBC OR (95% CI)[b]	*P*-value[c]	P_{FDR}
1p34.2	rs4233486	T/C	1.12 (1.02-1.23)	0.97 (0.95-0.98)	.003	.09
2p24.1	rs12710696	C/T	0.87 (0.79-0.95)	1.03 (1.01-1.04)	7.75×10^{-04}	.03
3p12.1	rs13066793	A/G	1.28 (1.08-1.51)	0.94 (0.91-0.97)	4.68×10^{-04}	.03
5p15.33	rs3215401	A/AG	1.10 (1.00-1.21)	0.93 (0.91-0.95)	7.63×10^{-04}	.03
6q25	rs9397437	G/A	1.58 (1.34-1.87)	1.17 (1.14-1.21)	4.15×10^{-04}	.03
9q31.2	rs10816625	A/G	0.85 (0.71-1.03)	1.11 (1.07-1.15)	.004	.09
10q26.13	rs2981578	T/C	1.08 (0.99-1.18)	1.23 (1.21-1.25)	.004	.09
14q24.1	rs2588809	C/T	1.59 (1.41-1.78)	1.06 (1.03-1.08)	1.25×10^{-10}	2.15×10^{-08}

[a] Alleles are shown as major/minor allele based on control frequencies.

[b] ORs for FBC from (16).

[c] *P*-value for statistical significance of the difference between MBC and FBC log ORs.

Table 3. Four FBC predisposition loci at which variants correlated at $r^2 \geq 0.10$ with a published FBC susceptibility SNP were more statistically significantly associated with MBC than the lead FBC SNP.

Cytoband	SNP[a]	Alleles[b]	Stage	Control MAF	Case MAF	OR (95% CI)	P-value[c]
6q25.1	rs3757322	T/G	GWAS	0.33	0.37	1.23 (1.12-1.35)	1.11×10^{-05}
			Replication	0.33	0.39	1.32 (1.15-1.52)	9.53×10^{-05}
			Joint	-	-	1.26 (1.16-1.36)	6.23×10^{-09}
	rs146723925	GAA/G	GWAS	0.35	0.39	1.23 (1.13-1.35)	7.73×10^{-06}
	$r^2 = 0.89$		Replication	-	-	Failed assay design	-
			Joint	-	-	-	-
6q25.1	rs9397437	G/A	GWAS	0.07	0.10	1.58 (1.34-1.87)	4.22×10^{-08}
			Replication	0.07	0.10	1.33 (1.05-1.69)	.02
			Joint	-	-	1.50 (1.31-1.71)	5.29×10^{-09}
	rs9383938	G/T	GWAS	0.08	0.11	1.60 (1.36-1.89)	1.63×10^{-08}
	$r^2 = 0.83$		Replication	0.09	0.11	1.30 (1.04-1.63)	.02
			Joint	-	-	1.47 (1.30-1.67)	2.93×10^{-09}
10p12.31	rs7072776	G/A	GWAS	0.27	0.30	1.17 (1.06-1.29)	.002
			Replication	0.28	0.31	1.15 (0.99-1.33)	.06
			Joint	-	-	1.16 (1.07-1.26)	2.46×10^{-04}
	rs2183271	T/C	GWAS	0.36	0.41	1.24 (1.13-1.36)	3.50×10^{-06}
	$r^2 = 0.68$		Replication	0.36	0.40	1.18 (1.02-1.35)	.02
			Joint	-	-	1.22 (1.13-1.31)	2.69×10^{-07}
11q13.3	rs75915166	C/A	GWAS	0.06	0.08	1.52 (1.25-1.83)	1.64×10^{-05}
			Replication	0.05	0.08	1.56 (1.19-2.04)	.001
			Joint	-	-	1.53 (1.31-1.79)	7.71×10^{-08}
	rs78540526	C/T	GWAS	0.07	0.10	1.58 (1.34-1.87)	7.38×10^{-08}
	$r^2 = 0.63$		Replication	0.06	0.10	1.68 (1.32-2.14)	2.45×10^{-05}
			Joint	-	-	1.61 (1.40-1.85)	1.06×10^{-11}

[a] For each locus the MBC effect estimates and association statistics for the lead FBC SNP are shown, followed by the estimates, correlation coefficient and association statistics for the correlated variant that was more strongly associated with MBC.

[b] Alleles are shown as major/minor allele based on control frequencies.

[c] MBC *P*-values were derived from fixed-effects inverse variance-weighted meta-analysis (GWAS and Joint) and from multiple logistic regression, adjusted for study (Replication). All tests were two-sided.

[-] Control and case MAFs were not calculated for meta-analysed SNPs at the joint analysis stage.

Table 4. Association between 313-SNP PRSs and male breast cancer risk.

SNP weights[a]	Quintile	No. of Controls[b]	Male			Female		
			No. of Cases	OR (95% CI)	*P*-value	No. of Cases	OR (95% CI)	*P*-value
Overall FBC	1st	533	124	1.00 (Ref)		165	1.00 (Ref)	
	2nd	532	227	1.83 (1.43-2.35)	1.92×10^{-06}	251	1.52 (1.21-1.92)	3.35×10^{-04}
	3rd	533	244	1.97 (1.54-2.52)	8.07×10^{-08}	340	2.06 (1.65-2.57)	1.53×10^{-10}
	4th	532	306	2.47 (1.94-3.15)	1.72×10^{-13}	357	2.17 (1.74-2.70)	5.67×10^{-12}
	5th	533	479	3.86 (3.07-4.87)	2.08×10^{-30}	558	3.38 (2.74-4.18)	1.17×10^{-29}
	Trend[c]	2,663	1,380	1.55 (1.45-1.66)	3.54×10^{-37}	1,671	1.51 (1.42-1.61)	4.58×10^{-37}
ER-positive FBC	1st	533	120	1.00 (Ref)		167	1.00 (Ref)	
	2nd	532	229	1.91 (1.49-2.46)	4.37×10^{-07}	254	1.52 (1.21-1.92)	3.17×10^{-04}
	3rd	533	243	2.03 (1.58-2.60)	2.97×10^{-08}	312	1.87 (1.49-2.33)	3.95×10^{-08}
	4th	532	307	2.56 (2.01-3.27)	3.01×10^{-14}	393	2.36 (1.90-2.93)	1.02×10^{-14}
	5th	533	481	4.01 (3.17-5.06)	1.91×10^{-31}	545	3.26 (2.64-4.03)	4.10×10^{-28}
	Trend[c]	2,663	1,380	1.55 (1.45-1.66)	3.54×10^{-37}	1,671	1.50 (1.41-1.60)	1.27×10^{-36}
ER-negative FBC	1st	533	175	1.00 (Ref)		201	1.00 (Ref)	
	2nd	532	204	1.17 (0.92-1.48)	.20	244	1.22 (0.97-1.52)	.08
	3rd	533	280	1.60 (1.28-2.00)	3.85×10^{-05}	354	1.76 (1.43-2.17)	1.39×10^{-07}
	4th	532	302	1.73 (1.39-2.16)	1.28×10^{-06}	368	1.83 (1.49-2.26)	1.43×10^{-08}
	5th	533	419	2.39 (1.93-2.96)	1.06×10^{-15}	504	2.51 (2.05-3.07)	6.56×10^{-19}
	Trend[c]	2,663	1,380	1.37 (1.29-1.47)	6.92×10^{-21}	1,671	1.38 (1.29-1.47)	1.02×10^{-23}

[a] Weights for the 313 SNPs in the PRS for overall, ER-positive and ER-negative FBC were obtained from (20).

[b] 2,663 males and females from the UK-58BC were used as UK population representative controls in the PRS analysis.

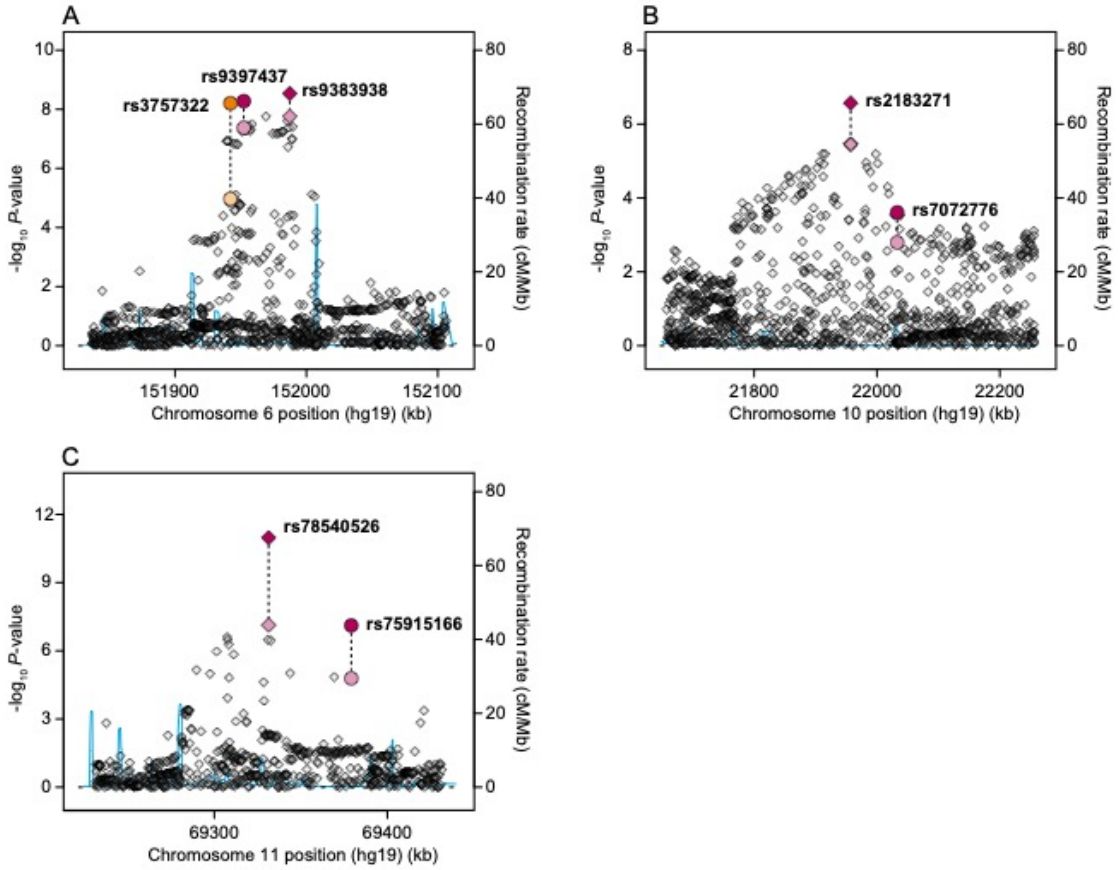
[c] OR per standard deviation increase in the PRS.

Figure Legends

Figure 1. Regional association plots for 6q25.1 (A), 10p12.31 (B) and 11q13.3 (C) male breast cancer risk loci. Each point represents an individual SNP sorted on the x-axis by physical position based on NCBI build 37 of the human genome and plotted by $-\log_{10}$ *P*-value on the y-axis. Recombination rates, estimated using HapMap data, are plotted in blue. For each region, the published female breast cancer predisposition SNP is plotted as a circle, alongside the variant most strongly associated with male breast cancer, plotted as a diamond. In instances where there are multiple independent predisposition loci at the same genomic region, pairs of SNPs are grouped by colour. Lighter colours represent the GWAS *P*-value and darker colours the joint *P*-value for the top SNPs. All statistical tests were two-sided.

Figure 2: Distributions of the 313-SNP PRS in 1,380 MBC cases, 1,671 FBC cases and 2,663 controls. PRS were standardised to mean = 0, SD = 1 using 2,663 controls from the UK-58C. The mean PRS was 0.44 in males and 0.41 in females.

Figure 1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rs9397437
rs9383938
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Recombination rate (cM/Mb)
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B
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rs7072776
-log10 P-value
Recombination rate (cM/Mb)
21800
22000
22200
Chromosome 10 position (hg19) (kb)
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69300
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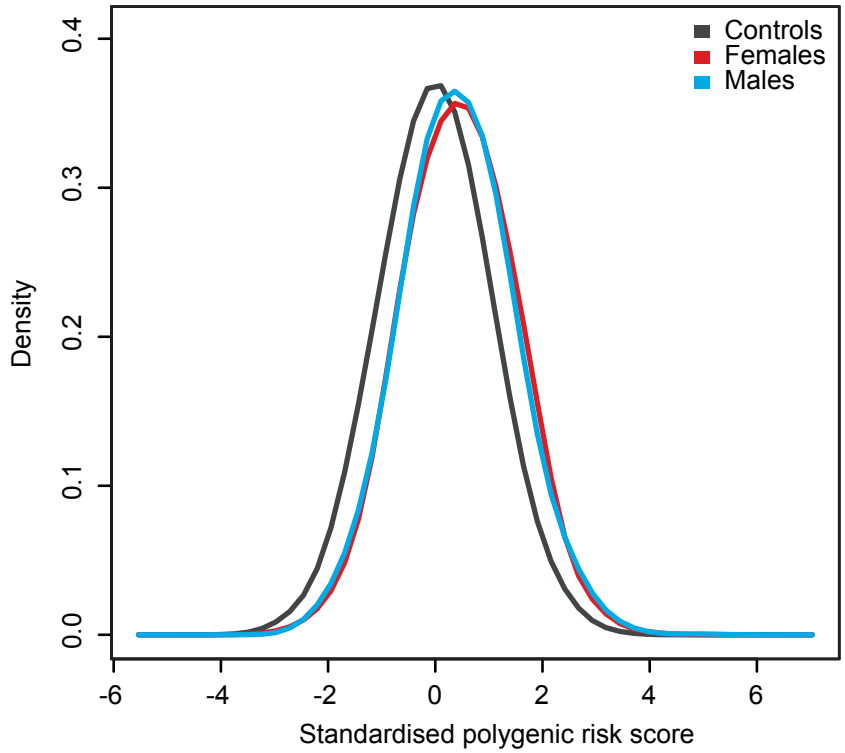
Chromosome 11 position (hg19) (kb)

Figure 2


Controls
Females
Males
Density
0.0
0.1
0.2
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0.4
-6
-4
-2
0
2
4
6
Standardised polygenic risk score

Supplementary Methods

Description of studies contributing to the discovery GWAS analysis

Breast Cancer Now Male Breast Cancer Study (UK-BCN-MBCS)

The UK-BCN-MBCS is a national population-based case-control study of male breast cancer in England and Wales that was established at the Institute of Cancer Research (ICR), London, in 2007 to investigate the aetiology of breast cancer in men and to illuminate, from a novel angle, aetiology in women. Potential cases were all men resident in England and Wales with invasive or *in situ* breast cancer diagnosed at ages 18-79 since 1st January 2005. Cases were ascertained from regional cancer registries and directly from consultants. Cases undertook a structured interview with a study research nurse, who collected either a blood sample or a sputum sample for DNA extraction. Ninety-one percent of cases enrolled in the study provided a sample for DNA extraction. UK-BCN-MBCS controls were from two sources – male non-blood relatives of cases, and male spouses of women taking part in the UK-GS (described below). Controls were stratum-matched with cases, initially 1:1 and subsequently two controls per three cases, for economy. The study was approved by the South East Multicentre Research Ethics Committee. Following QC analysis, the discovery dataset used here for association analysis comprised 1,116 cases and 259 controls from UK-BCN-MBCS.

City of Hope Male Breast Cancer Study (US-CoH)

The US-CoH cases have been described elsewhere (1). Briefly, 83 cases were ascertained from state cancer registries in Utah and the surrounding intermountain states (Colorado, Idaho and Wyoming). A small number of additional cases were ascertained via an online male breast cancer support group (18 cases), referrals from physicians (four cases) and from family members (ten cases). The participants were enrolled under Institutional Review Board approval and all signed informed consent. The ten cases

referred by family members were from breast cancer families and the remaining cases were unselected for age or family history of breast cancer. The average age at diagnosis was 60 years with a range from 28 to 93 years. Following QC analysis, the discovery dataset used here for association analysis comprised 112 cases from US-CoH.

University of Cambridge Male Breast Cancer Study (UK-UoC)

The UK-UoC cases were obtained from a population-based study of male breast cancers that were diagnosed in areas covered by the East Anglia, Trent and the West Midlands cancer registries between 1991 and 2010 (2). Participants completed a detailed epidemiological questionnaire and provided a blood sample for genetic analysis. The study was approved by the National Research Ethics Service East of England – Cambridge South ethics committee. One hundred and sixty-five eligible patients were identified, of which 138 had samples available for genotyping in this study. Age at diagnosis of breast cancer of the 138 genotyped cases ranged from 29 to 87 years with a mean of 61 years. Following QC analysis, the discovery dataset used here for association analysis comprised 129 cases from UK-UoC.

University of Leeds Male Breast Cancer Study (UK-UoL)

The UK-UoL cases were ascertained from a case control study of histologically confirmed male breast cancer conducted in the Yorkshire, Trent and North-West regions of the UK between 1983 and 1990 (3). The ages of the genotyped cases ranged from 41 to 80 years, with mean 62 years, diagnosed between 1983 and 1990. Following QC analysis, the discovery dataset used here for association analysis comprised 23 cases from UK-UoL.

Generations Study (UK-GS)

The Generations Study (UK-GS) is a long-term prospective cohort study of breast cancer aetiology involving >113,000 women from the UK, recruited between 2003 and 2013 (4). The study cohort consists of women aged 16 years or older at entry who were identified from either a list of supporters of Breakthrough Breast Cancer (the charity who funded the study), by expression of interest via website and telephone lines when the study launched and finally by participant nomination of female friends and family. Upon registering to join the cohort, women were provided with a detailed epidemiological questionnaire and blood collection pack. Venepuncture was typically performed at the cohort members' general practice surgery then blood samples were mailed to the study laboratory for recovery of buffy coat and plasma prior to long-term LN2 storage. The present study utilised genotype data from UK-GS controls that were generated using Oncoarray as part of the Breast Cancer Association Consortium (BCAC). Following QC analysis, the discovery dataset used for association analysis comprised 698 controls from UK-GS.

1958 British Birth Cohort (UK-58BC)

The 1958 British Birth Cohort is a cohort study of 17,415 UK individuals born in a single week of 1958 which has been extensively described (5) and for which a subset of healthy individuals was subject to genome-wide genotyping as part of the Wellcome Trust Case-Control Consortium (WTCCC) (6). Access to individual-level genotype data is available by application to the WTCCC Data Access Committee. The WTCCC resource has been widely used to provide a geographically representative sample of SNP genotypes from UK individuals of predominantly European ancestry for genetic association studies. Following QC analysis, the discovery dataset used for association analysis comprised 1,367 male and 1,296 female controls from UK-58BC.

Supplementary References

1. Ding YC, Steele L, Kuan CJ, *et al*. Mutations in BRCA2 and PALB2 in Male Breast Cancer Cases from the United States. Breast Cancer Res Treat 2011; 126(3):771-8.

2. Basham VM, Lipscombe JM, Ward JM, *et al*. BRCA1 and BRCA2 Mutations in a Population-Based Study of Male Breast Cancer. Breast Cancer Res 2002; 4(1):R2.

3. Mavraki E, Gray IC, Bishop DT, *et al*. Germline BRCA2 Mutations in Men With Breast Cancer. Br J Cancer 1997; 76(11):1428-31.

4. Swerdlow AJ, Jones ME, Schoemaker MJ, *et al*. The Breakthrough Generations Study: Design of a Long-Term UK Cohort Study to Investigate Breast Cancer Aetiology. Br J Cancer 2011; 105(7):911-7.

5. Power C, Elliott J. Cohort Profile: 1958 British Birth Cohort (National Child Development Study). Int J Epidemiol 2006; 35(1):34-41.

6. Wellcome Trust Case-Control Consortium. Genome-wide Association Study of 14,000 Cases of Seven Common Diseases and 3,000 Shared Controls. Nature 2007; 447(7145):661-78.

7. Orr N, Lemnrau A, Cooke R, et al. Genome-wide association study identifies a common variant in RAD51B associated with male breast cancer risk. Nat Genet 2012;44(11):1182-4.

8. Michailidou K, Lindstrom S, Dennis J*, et al.* Association analysis identifies 65 new breast cancer risk loci. Nature 2017;551(7678):92-94.

Supplementary Table 1: Subjects for GWAS and validation

	Source	Status	Number	Source	Age (years; mean, range)	Years of diagnosis (cases)
Discovery	**UK-BCN-MBCS**	**Case**	1210	Population of England and Wales	64 (23-87)	2003-2016
		Control	264		64 (30-90)	-
	UK-UoL	**Case**	31	Population of Trent and Yorkshire, UK	62 (41-80)	1983-1990
	UK-UoC	**Case**	138	Population of West Midlands, Trent, and Eastern Cancer Registries	61 (29-87)	1991-2010
	US-CoH	**Case**	113	Population of USA	61 (28-93)	1963-2001
	UK-58BC	**Control**	2663	Population of England, Scotland and Wales	-	-
	UK-GS	**Control**	698	Population of UK	54 (22-81)	-
Replication	**KConFab, Australia**	**Case**	72	Population of Australia and New Zealand	61 (31-87)	1977-2011
		Control	70	Population of Australia and New Zealand	61 (37-92)	-
	Peter MacCallum Cancer Centre, Australia	**Case**	34	Hospital (PMCC familial cancer clinic)	66 (51-84)	1996-2010
		Control	-			-
	The Finnish Male Breast Cancer Study, Finland	**Case**	52	Hospital-based series (Helsinki, Oulu, Vaasa and Kuopio)	61 (30-80)	1985-2011
		Control	66	Adult blood donors from Finland	unknown	-
	University Hospital of Heraklion, Greece	**Case**	29	Hospital-based series (Athens and Heraklion)	58 (30-80)	1995-2012
		Control	31	Adult blood donors from Heraklion, Crete, Greece	unknown	
	Sheba Medical Centre, Israel	**Case**	33	Hospital-based series (Tel-Aviv)	65 (39-79)	2006-2011
		Control	37	Hospital-based (unrelated healthy visitors; Tel-Aviv)	66 (39-82)	-
	ISPO, Florence, Italy	**Case**	80	Population of Tuscany	65 (35-87)	1990-2011
		Control	89	Population of Tuscany	58 (43-65)	-
	Sapienza University of Rome, Italy	**Case**	32	Hospital-based series (Rome)	61 (22-79)	1986-2010
		Control	33	Hospital-based series (Rome)	60 (55-64)	-
	Erasmus MC, The Netherlands	**Case**	51	Breast cancer families from the South West of the Netherlands	57 (28-86)	1964-2009

		Control	49	Males from CF families who were spouses of at risk individuals	57 (28-86)	-
	Institute of Oncology Ljubljana, Slovenia	**Case**	34	Population of Slovenia	56 (17-86)	1970-2010
		Control	45	Population of Slovenia	35 (18-60)	-
	Santiago and Vigo University Hospitals, Galicia, Spain	**Case**	2	Population of Galicia, Spain	68 (49-88)	2000-2010
		Control	9	Population of Galicia, Spain	68 (49-88)	-
	Lund University, Sweden	**Case**	46	Hospital (Lund University Hospital)	63 (26-82)	1978-2010
		Control	39	Spouses of cancer patients who had no history of cancer	63 (44-77)	-
	BCN-MBCS, UK	**Case**	345	Population of England and Wales	64 (37-78)	2009-2011
		Control	558	Population of England and Wales	58 (32-86)	-

Supplementary Table 2: Sensitivity of MBC predisposition SNP ORs to inclusion of US-CoH cases.

	With US-CoH cases		US-CoH cases omitted	
SNP	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
rs9371545	1.61 (1.34-1.94)	6.59×10^{-07}	1.63 (1.34-1.98)	1.11×10^{-06}
rs3757322	1.20 (1.08-1.34)	6.24×10^{-04}	1.18 (1.05-1.31)	0.004
rs146723925	1.21 (1.09-1.34)	4.43×10^{-04}	1.19 (1.06-1.32)	0.002
rs9397437	1.59 (1.32-1.92)	1.29×10^{-06}	1.60 (1.31-1.94)	3.00×10^{-06}
rs9383938	1.54 (1.29-1.84)	1.99×10^{-06}	1.54 (1.28-1.85)	5.75×10^{-06}
rs7072776	1.14 (1.02-1.27)	0.02	1.20 (1.00-1.27)	0.04
rs2183271	1.22 (1.10-1.36)	1.37×10^{-04}	1.21 (1.09-1.35)	4.88×10^{-04}
rs75915166	1.58 (1.27-1.97)	3.41×10^{-05}	1.63 (1.03-2.05)	2.19×10^{-05}
rs78540526	1.68 (1.39-2.04)	1.47×10^{-07}	1.76 (1.44-2.15)	4.26×10^{-08}
rs554219	1.43 (1.23-1.67)	4.06×10^{-06}	1.47 (1.25-1.72)	2.11×10^{-06}

Supplementary Table 3: Sensitivity of MBC predisposition SNP ORs to inclusion of female UK-GS and UK-58BC controls.

	All controls		No female controls	
SNP	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
rs9371545	1.60 (1.36-1.89)	1.63×10^{-08}	1.58 (1.31-1.89)	1.13×10^{-06}
rs3757322	1.23 (1.12-1.35)	1.11×10^{-05}	1.22 (1.10-1.36)	2.06×10^{-04}
rs146723925	1.23 (1.13-1.35)	7.73×10^{-06}	1.21 (1.09-1.35)	3.53×10^{-04}
rs9397437	1.58 (1.34-1.87)	4.22×10^{-08}	1.54 (1.28-1.84)	4.66×10^{-06}
rs9383938	1.60 (1.36-1.89)	1.63×10^{-08}	1.53 (1.29-1.82)	1.65×10^{-06}
rs7072776	1.17 (1.06-1.29)	0.002	1.22 (1.09-1.37)	4.27×10^{-04}
rs2183271	1.24 (1.13-1.36)	3.50×10^{-06}	1.28 (1.15-1.42)	5.06×10^{-06}
rs75915166	1.52 (1.25-1.83)	1.64×10^{-05}	1.49 (1.21-1.84)	1.92×10^{-04}
rs78540526	1.58 (1.34-1.87)	7.38×10^{-08}	1.56 (1.30-1.88)	2.76×10^{-06}
rs554219	1.42 (1.24-1.62)	1.86×10^{-07}	1.40 (1.21-1.63)	1.08×10^{-05}

Supplementary Table 4: Association analysis of loci that attained genome-wide significance (*P*-value ≤ 5 x 10^{-08}) or promising signals of association (*P*-value ≤ 1 x 10^{-06}) in combined analysis of three GWAS datasets and an independent validation cohort.

Locus[a]		MAF[b]	Info	OR (95% CI)	*P*-value[c]	*P*-het[d]	BFDP[e]
rs3757322	GWAS 1	0.33 | 0.38	1	1.20 (1.08-1.34)	6.24 x 10^{-04}		
6q25.1	GWAS 2	0.32 | 0.37	1	1.27 (1.00-1.62)	0.05		
T/G	GWAS 3	0.28 | 0.35	1	1.42 (1.04-1.95)	0.03		
151942194	**Combined**			**1.23 (1.12-1.35)**	**1.11 x 10^{-05}**	**0.58**	
	Validation	0.33 | 0.39		1.32 (1.15-1.52)	9.53 x 10^{-05}		
	Overall (Fixed Effects)			**1.26 (1.16-1.36)**	**6.23 x 10^{-09}**	**0.62**	**8.20 x 10^{-04}**
rs146723925[f]	GWAS 1	0.35 | 0.4	0.984	1.21 (1.09-1.34)	4.20 x 10^{-04}		
6q25.1	GWAS 2	0.33 | 0.4	0.991	1.31 (1.03-1.66)	0.03		
GAA/G	GWAS 3	0.31 | 0.36	0.988	1.34 (0.98-1.84)	0.07		
151946173	**Combined**			**1.23 (1.13-1.35)**	**7.73 x 10^{-06}**	**0.73**	**0.54**
rs9397437	GWAS 1	0.07 | 0.1	0.994	1.59 (1.32-1.92)	1.30 x 10^{-06}		
6q25.1	GWAS 2	0.07 | 0.1	1	1.58 (1.03-2.42)	0.03		
G/A	GWAS 3	0.05 | 0.08	1	1.53 (0.87-2.69)	0.14		
151952332	**Combined**			**1.58 (1.34-1.87)**	**4.22 x 10^{-08}**	**0.99**	
	Validation	0.07 | 0.1		1.33 (1.05-1.69)	0.02		
	Overall (Fixed Effects)			**1.50 (1.31-1.71)**	**5.29 x 10^{-09}**	**0.70**	**0.009**
rs9371545[f]	GWAS 1	0.07 | 0.11	0.974	1.61 (1.34-1.94)	6.56 x 10^{-07}		
6q25.1	GWAS 2	0.07 | 0.11	0.996	1.63 (1.07-2.48)	0.02		
G/A	GWAS 3	0.05 | 0.08	0.982	1.50 (0.85-2.64)	0.16		
151969740	**Combined**			**1.60 (1.36-1.89)**	**1.63 x 10^{-08}**	**0.97**	**0.26**
rs9383938	GWAS 1	0.08 | 0.11	0.998	1.54 (1.29-1.84)	1.99 x 10^{-06}		
6q25.1	GWAS 2	0.08 | 0.12	1	1.69 (1.13-2.53)	0.01		
G/T	GWAS 3	0.06 | 0.09	1	1.57 (0.93-2.66)	0.09		
151987357	**Combined**			**1.60 (1.36-1.89)**	**1.63 x 10^{-08}**	**0.91**	
	Validation	0.09 | 0.11		1.30 (1.04-1.63)	0.02		

	Overall (Fixed Effects)			**1.47 (1.30-1.67)**	**2.93 x 10^{-09}**	**0.58**	**0.01**
rs2183271	GWAS 1	0.36 | 0.41	1	1.22 (1.1-1.36)	1.37 x 10^{-04}		
10p12.31	GWAS 2	0.37 | 0.4	1	1.15 (0.91-1.46)	0.26		
T/C	GWAS 3	0.32 | 0.42	0.971	1.55 (1.15-2.08)	0.004		
21957229	**Combined**			**1.24 (1.13-1.36)**	**3.50 x 10^{-06}**	**0.27**	
	Validation	0.36 | 0.4		1.18 (1.02-1.35)	0.02		
	Overall (Fixed Effects)			**1.22 (1.13-1.31)**	**2.69 x 10^{-07}**	**0.39**	**0.006**
rs7072776	GWAS 1	0.27 | 0.3	1	1.14 (1.02-1.27)	0.02		
10p12.31	GWAS 2	0.28 | 0.32	1	1.22 (0.95-1.56)	0.12		
G/A	GWAS 3	0.25 | 0.31	1	1.37 (1-1.87)	0.05		
22032942	**Combined**			**1.17 (1.06-1.29)**	**0.002**	**0.52**	
	Validation	0.28 | 0.31		1.15 (0.99-1.33)	0.06		
	Overall (Fixed Effects)			**1.16 (1.07-1.26)**	**2.46 x 10^{-04}**	**0.72**	**0.93**
rs78540526	GWAS 1	0.07 | 0.1	0.97	1.69 (1.39-2.05)	1.07 x 10^{-07}		
11q13.3	GWAS 2	0.08 | 0.1	0.995	1.33 (0.89-2.00)	0.17		
C/T	GWAS 3	0.07 | 0.08	1	1.25 (0.72-2.18)	0.42		
69331418	**Combined**			**1.58 (1.34-1.87)**	**7.38 x 10^{-08}**	**0.40**	
	Validation	0.06 | 0.1		1.68 (1.32-2.14)	2.45 x 10^{-05}		
	Overall (Fixed Effects)			**1.61 (1.4-1.85)**	**1.06 x 10^{-11}**	**0.57**	**0.001**
rs554219	GWAS 1	0.12 | 0.16	0.997	1.43 (1.23-1.67)	4.06 x 10^{-06}		
11q13.3	GWAS 2	0.13 | 0.17	1	1.35 (0.97-1.87)	0.09		
C/G	GWAS 3	0.11 | 0.15	0.999	1.45 (0.94-2.25)	0.07		
69331642	**Combined**			**1.42 (1.24-1.62)**	**1.86 x 10^{-07}**	**0.94**	
	Validation	0.11 | 0.16		1.52 (1.25-1.84)	2.65 x 10^{-05}		
	Overall (Fixed Effects)			**1.45 (1.3-1.62)**	**2.86 x 10^{-11}**	**0.94**	**2.77 x 10^{-04}**
rs75915166	GWAS 1	0.06 | 0.08	0.941	1.6 (1.28-1.98)	2.59 x 10^{-05}		
11q13.3	GWAS 2	0.06 | 0.07	1	1.27 (0.79-2.04)	0.32		
C/A	GWAS 3	0.05 | 0.06	1	1.27 (0.70-2.58)	0.38		

69379161	**Combined**			**1.52 (1.25-1.83)**	**1.64 x 10^{-05}**	**0.64**	
	Validation	0.05 | 0.08		1.56 (1.19-2.04)	0.001		
	Overall (Fixed Effects)			**1.53 (1.31-1.79)**	**7.71 x 10^{-08}**	**0.82**	**0.32**
rs1022979[g]	GWAS 1	0.17 | 0.23	0.998	1.55 (1.36-1.76)	3.82 x 10^{-11}		
14q24.1	GWAS 2	0.16 | 0.26	0.999	1.81 (1.36-2.41)	4.86 x 10^{-05}		
T/A	GWAS 3	0.15 | 0.24	0.999	1.75 (1.22-2.52)	0.003		
68624639	**Combined**			**1.60 (1.43-1.79)**	**1.53 x 10^{-16}**	**0.55**	**4.63 x 10^{-08}**
rs4407020	GWAS 1	0.22 | 0.27	1	1.29 (1.15-1.45)	2.52 x 10^{-05}		
15q24	GWAS 2	0.21 | 0.28	0.905	1.60 (1.20-2.13)	0.001		
T/G	GWAS 3	0.24 | 0.26	0.987	1.10 (0.79-1.54)	0.56		
70818373	**Combined**			**1.31 (1.18-1.45)**	**4.51 x 10^{-07}**	**0.23**	
	Validation	0.24 | 0.24		0.93 (0.78-1.10)	0.39		
	Overall (Fixed Effects)			**1.19 (1.09-1.31)**	**1.02 x 10^{-04}**	**2.85 x 10^{-03}**	**0.94**
rs35850695[g]	GWAS 1	0.26 | 0.33	0.989	1.44 (1.29-1.62)	2.11 x 10^{-10}		
16q12.1	GWAS 2	0.26 | 0.31	1	1.27 (0.99-1.63)	0.06		
G/A	GWAS 3	0.27 | 0.33	0.996	1.29 (0.96-1.72)	0.09		
52574343	**Combined**			**1.40 (1.27-1.54)**	**1.57 x 10^{-11}**	**0.54**	**1.47 x 10^{-05}**

[a] SNP alleles presented as reference / effect.

[b] MAFs are presented as control MAF | case MAF.

[c] All tests were two-sided.

[d] *P*-value for Cochran's Q-test for heterogeneity between the GWAS datasets and the validation dataset.

[e] Bayesian false discovery probabilities for each association, assuming a maximum likely OR of 1.2 and a prior of 0.1%; the BFDP noteworthiness threshold was 0.8.

[f] SNP rs9371545 failed assay design for replication genotyping therefore validation analysis was based on the next most significant correlated SNP that passed assay design, rs9383938 (r^2 with rs9371545 = 0.83).

[g] SNPs rs1022979 and rs35850695 are strongly correlated with previously published MBC risk SNPs at 14q24.1 and 16q12.1 (7) respectively and therefore were not subject to validation analysis.

Supplementary Table 6: Comparison of effect estimates of FBC SNPs for male and female breast cancer. Differences are shown for overall FBC, ER-positive FBC and ER-negative FBC.

					Overall FBC			ER+ FBC			ER- FBC		
Cytoband	SNP	Alleles	OR MBC	*P* MBC	OR FBC[a]	*P* Diff[b]	*P* FDR	OR ER+[a]	*P* Diff[b]	*P* FDR	OR ER-[a]	*P* Diff[b]	*P* FDR
1p36.22	rs616488	A/G	0.87 (0.80-0.96)	4.93E-03	0.94 (0.93-0.96)	0.07	0.38	0.96 (0.94-0.98)	0.03	0.19	0.89 (0.86-0.92)	0.62	0.88
1p36.13	rs2992756	C/T	1.16 (1.06-1.27)	1.22E-03	1.06 (1.04-1.08)	0.06	0.34	1.07 (1.05-1.09)	0.09	0.39	1.03 (1.00-1.07)	0.01	0.12
1p34.2	rs4233486	T/C	1.12 (1.02-1.23)	0.02	0.97 (0.95-0.98)	3.27E-03	0.09	0.97 (0.95-0.99)	3.27E-03	0.05	0.97 (0.94-1.00)	4.28E-03	0.05
1p34.2	rs79724016	T/G	0.88 (0.67-1.15)	0.34	0.93 (0.88-0.97)	0.7	0.87	0.91 (0.86-0.96)	0.81	0.91	0.89 (0.98-1.07)	0.94	0.99
1p34.1	rs1707302	G/A	0.99 (0.91-1.09)	0.91	0.96 (0.95-0.98)	0.48	0.78	0.96 (0.94-0.98)	0.49	0.77	1.01 (0.98-1.04)	0.66	0.88
1p32.3	rs140850326	I*/C	0.98 (0.89-1.07)	0.6	0.97 (0.95-0.99)	0.84	0.91	0.97 (0.95-0.99)	0.84	0.91	0.96 (0.93-0.99)	0.69	0.88
1p22.3	rs17426269	G/A	1.05 (0.93-1.18)	0.47	1.05 (1.02-1.07)	1	1	1.06 (1.03-1.09)	0.88	0.92	1.04 (0.99-1.08)	0.89	0.95
1p13.2	rs11552449	C/T	1.13 (1.01-1.27)	0.03	1.04 (1.01-1.06)	0.16	0.49	1.04 (1.01-1.06)	0.16	0.48	1.04 (1.00-1.08)	0.17	0.59
1p12	rs7529522	T/C	1.02 (0.92-1.13)	0.73	1.06 (1.04-1.08)	0.47	0.77	1.07 (1.04-1.09)	0.38	0.72	1.05 (1.02-1.09)	0.6	0.88
1p11.2	rs11249433	A/G	1.01 (0.92-1.10)	0.85	1.11 (1.09-1.13)	0.05	0.31	1.14 (1.12-1.16)	0.01	0.13	1.02 (0.99-1.06)	0.84	0.94
1q21.1	rs12405132	C/T	0.98 (0.90-1.08)	0.75	0.97 (0.95-0.99)	0.82	0.91	0.97 (0.95-0.99)	0.82	0.91	1.00 (0.96-1.03)	0.68	0.88
1q21.2	rs12048493	A/C	1.08 (0.98-1.18)	0.12	1.04 (1.02-1.06)	0.46	0.76	1.04 (1.02-1.07)	0.46	0.75	1.05 (1.02-1.09)	0.59	0.88
1q22	rs4971059	G/A	1.04 (0.95-1.14)	0.34	1.05 (1.03-1.07)	0.84	0.91	1.06 (1.04-1.09)	0.69	0.86	1.03 (1.00-1.07)	0.84	0.94
1q32.1	rs35383942	C/T	1.19 (0.99-1.43)	0.06	1.12 (1.08-1.17)	0.53	0.8	1.10 (1.05-1.15)	0.42	0.72	1.15 (1.08-1.23)	0.73	0.89
1q32.1	rs6678914	G/A	1.03 (0.94-1.13)	0.5	1.00 (0.99-1.02)	0.53	0.8	1.02 (1.00-1.04)	0.84	0.91	0.94 (0.91-0.97)	0.06	0.36
1q32.19	rs4951011	A/G	0.99 (0.88-1.12)	0.85	1.04 (1.02-1.07)	0.42	0.72	1.03 (1.01-1.06)	0.52	0.77	1.07 (1.02-1.11)	0.23	0.64
1q32.1	rs4245739	A/C	0.94 (0.85-1.03)	0.18	1.02 (1.00-1.04)	0.12	0.41	1.00 (0.98-1.02)	0.24	0.58	1.12 (1.09-1.17)	9.87E-04	0.02
1q41	rs11117758	G/A	1.08 (0.97-1.21)	0.15	0.95 (0.93-0.97)	0.02	0.17	0.94 (0.92-0.96)	0.01	0.13	0.98 (0.95-1.02)	0.09	0.43
1q43	rs72755295	A/G	0.88 (0.66-1.16)	0.37	1.15 (1.09-1.20)	0.07	0.38	1.16 (1.10-1.23)	0.06	0.35	1.09 (1.00-1.19)	0.16	0.57
2p25.1	rs113577745	C/G	1.01 (0.87-1.17)	0.93	1.08 (1.05-1.11)	0.39	0.72	1.08 (1.04-1.10)	0.39	0.72	1.06 (1.01-1.12)	0.55	0.87
2p24.1	rs12710696	C/T	0.87 (0.79-0.95)	2.76E-03	1.03 (1.01-1.04)	7.75E-04	0.03	1.01 (0.99-1.04)	2.99E-03	0.05	1.04 (1.00-1.07)	7.81E-04	0.02
2p23.3	rs6725517	A/G	0.91 (0.83-0.99)	0.03	0.96 (0.94-0.98)	0.27	0.61	0.97 (0.95-0.99)	0.18	0.48	0.93 (0.90-0.96)	0.66	0.88
2p23.2	rs4577244	C/T	1.00 (0.90-1.11)	0.98	1.01 (0.99-1.03)	0.86	0.91	1.05 (1.02-1.07)	0.38	0.72	0.93 (0.89-0.96)	0.21	0.63
2q13	rs71801447	CTTATGTT/C	1.00 (0.84-1.20)	0.96	1.09 (1.05-1.13)	0.34	0.7	1.09 (1.05-1.13)	0.34	0.7	1.05 (0.99-1.12)	0.6	0.88
2q14.1	rs4849887	C/T	0.96 (0.82-1.11)	0.55	0.91 (0.88-0.94)	0.52	0.8	0.92 (0.89-0.96)	0.6	0.81	0.85 (0.81-0.90)	0.15	0.55
2q31.1	rs2016394	G/A	1.07 (0.98-1.17)	0.12	0.95 (0.94-0.97)	0.01	0.1	0.94 (0.92-0.96)	5.00E-03	0.07	1.00 (0.97-1.03)	0.15	0.55
2q31.1	rs1550623	A/G	1.00 (0.89-1.12)	0.94	0.95 (0.93-0.98)	0.4	0.72	0.94 (0.91-0.97)	0.32	0.68	1.00 (0.95-1.04)	1	1
2q33.1	rs1830298	T/C	1.09 (0.98-1.20)	0.1	1.06 (1.04-1.08)	0.61	0.84	1.05 (1.03-1.08)	0.5	0.77	1.08 (1.04-1.12)	0.87	0.94
2q35	rs4442975	G/T	0.92 (0.85-1.01)	0.07	0.89 (0.87-0.90)	0.43	0.73	0.87 (0.85-0.88)	0.18	0.48	0.94 (0.92-0.98)	0.61	0.88
2q35	rs34005590	C/A	0.98 (0.80-1.20)	0.83	0.82 (0.79-0.86)	0.09	0.38	0.80 (0.76-0.84)	0.06	0.33	0.98 (0.91-1.05)	1	1
2q35	rs16857609	C/T	1.12 (1.01-1.23)	0.02	1.06 (1.04-1.09)	0.3	0.65	1.07 (1.04-1.08)	0.4	0.72	1.07 (1.03-1.10)	0.42	0.77
2q36.3	rs12479355	A/G	0.90 (0.81-1.01)	0.06	0.96 (0.94-0.98)	0.24	0.59	0.96 (0.93-0.98)	0.25	0.59	1.00 (0.96-1.04)	0.07	0.36
3p26.1	rs6762644	A/G	0.98 (0.89-1.07)	0.58	1.05 (1.03-1.07)	0.17	0.5	1.06 (1.04-1.08)	0.12	0.45	1.04 (1.01-1.08)	0.25	0.64

					Overall FBC			ER+ FBC			ER- FBC		
Cytoband	**SNP**	**Alleles**	**OR MBC**	***P* MBC**	**OR FBC[a]**	***P* Diff[b]**	***P* FDR**	**OR ER+[a]**	***P* Diff[b]**	***P* FDR**	**OR ER-[a]**	***P* Diff[b]**	***P* FDR**
3p24.1	rs4973768	C/T	1.12 (1.03-1.23)	8.84E-03	1.11 (1.09-1.13)	0.84	0.91	1.12 (1.10-1.14)	1	1	1.04 (1.01-1.07)	0.1	0.45
3p.24.1	rs12493607	G/C	1.03 (0.94-1.13)	0.5	1.05 (1.03-1.07)	0.69	0.86	1.06 (1.04-1.08)	0.55	0.77	1.00 (0.96-1.03)	0.56	0.88
3p21.31	rs6796502	G/A	1.05 (0.91-1.21)	0.48	0.92 (0.89-0.95)	0.08	0.38	0.92 (0.89-0.95)	0.08	0.39	0.92 (0.87-0.97)	0.09	0.43
3p14.1	rs1053338	A/G	1.11 (0.98-1.27)	0.11	1.05 (1.02-1.07)	0.39	0.72	1.03 (1.01-1.06)	0.24	0.59	1.03 (0.99-1.08)	0.26	0.66
3p13	rs6805189	T/C	1.02 (0.94-1.12)	0.59	0.97 (0.95-0.99)	0.24	0.59	0.96 (0.94-0.98)	0.16	0.48	1.00 (0.97-1.03)	0.66	0.88
3p12.1	rs13066793	A/G	1.28 (1.08-1.51)	5.24E-03	0.94 (0.91-0.97)	4.68E-04	0.03	0.93 (0.89-0.96)	3.60E-04	0.02	0.96 (0.91-1.02)	1.55E-03	0.03
3p12.1	rs9833888	G/T	1.15 (1.04-1.28)	6.62E-03	1.06 (1.04-1.08)	0.12	0.41	1.07 (1.04-1.09)	0.18	0.48	1.01 (0.98-1.05)	0.02	0.12
3q23	rs34207738	CTT/C	1.03 (0.94-1.13)	0.49	1.06 (1.04-1.08)	0.55	0.8	1.06 (1.04-1.08)	0.55	0.77	1.03 (1.00-1.07)	1	1
3q26.31	rs58058861	G/A	1.09 (0.98-1.21)	0.12	1.06 (1.04-1.09)	0.61	0.84	1.07 (1.04-1.10)	0.74	0.9	1.00 (0.96-1.04)	0.14	0.55
4p14	rs6815814	A/C	1.04 (0.93-1.16)	0.48	1.06 (1.04-1.08)	0.74	0.9	1.05 (1.03-1.08)	0.87	0.92	1.06 (1.02-1.10)	0.75	0.9
4q21.23	4:84370124	TA/TAA	1.05 (0.95-1.15)	0.33	1.04 (1.02-1.05)	0.85	0.91	1.04 (1.01-1.06)	0.86	0.91	1.03 (1.00-1.06)	0.72	0.89
4q22.1	rs10022462	C/T	1.03 (0.95-1.13)	0.47	1.04 (1.02-1.06)	0.82	0.91	1.04 (1.02-1.06)	0.82	0.91	1.01 (0.98-1.05)	0.66	0.88
4q24	rs9790517	C/T	1.13 (1.02-1.27)	0.02	1.04 (1.01-1.06)	0.13	0.42	1.05 (1.03-1.08)	0.17	0.48	0.98 (0.94-1.02)	0.01	0.1
4q28.1	rs77528541	G/T	0.86 (0.76-0.98)	0.03	0.95 (0.92-0.97)	0.13	0.42	0.94 (0.92-0.97)	0.16	0.48	0.94 (0.90-0.99)	0.18	0.59
4q34.1	rs6828523	C/A	0.82 (0.72-0.95)	7.30E-03	0.91 (0.88-0.93)	0.13	0.42	0.88 (0.85-0.91)	0.3	0.67	1.00 (0.95-1.05)	5.40E-03	0.06
5p15.33	rs116095464	T/C	1.11 (0.92-1.35)	0.28	1.06 (1.02-1.10)	0.64	0.86	1.07 (1.02-1.12)	0.71	0.88	1.03 (0.96-1.11)	0.46	0.79
5p15.33	rs10069690	C/T	0.98 (0.89-1.08)	0.66	1.06 (1.04-1.08)	0.12	0.41	1.02 (1.00-1.05)	0.43	0.72	1.19 (1.14-1.23)	3.08E-04	7.57E-03
5p15.33	rs3215401	A/AG	1.10 (1.00-1.21)	0.06	0.93 (0.91-0.95)	7.63E-04	0.03	0.95 (0.93-0.97)	3.26E-03	0.05	0.88 (0.85-0.91)	1.62E-05	9.27E-04
5p15.1	rs13162653	G/T	1.00 (0.91-1.09)	0.97	0.99 (0.97-1.01)	0.84	0.91	0.99 (0.97-1.01)	0.84	0.91	0.98 (0.95-1.01)	0.69	0.88
5p13.3	rs2012709	C/T	1.02 (0.93-1.11)	0.66	1.02 (1.00-1.04)	1	1	1.03 (1.01-1.05)	0.84	0.91	0.98 (0.95-1.01)	0.42	0.77
5p12	rs10941679	A/G	1.27 (1.15-1.40)	3.03E-06	1.15 (1.13-1.18)	0.05	0.31	1.18 (1.16-1.21)	0.15	0.48	1.03 (1.00-1.07)	7.37E-05	2.53E-03
5q11.1	rs72749841	T/C	1.01 (0.88-1.17)	0.84	0.93 (0.91-0.96)	0.25	0.6	0.94 (0.90-0.97)	0.33	0.68	0.99 (0.94-1.04)	0.79	0.94
5q11.1	rs35951924	A/AT	1.02 (0.92-1.13)	0.68	0.95 (0.93-0.97)	0.19	0.53	0.95 (0.93-0.97)	0.19	0.48	0.96 (0.93-1.00)	0.27	0.67
5q11.2	rs62355902	A/T	0.99 (0.87-1.11)	0.82	1.18 (1.15-1.21)	0.01	0.1	1.22 (1.19-1.25)	1.86E-03	0.05	1.06 (1.02-1.11)	0.32	0.71
5q11.2	rs10472076	T/C	1.06 (0.97-1.16)	0.2	1.03 (1.01-1.04)	0.54	0.8	1.03 (1.01-1.05)	0.54	0.77	1.03 (1.00-1.07)	0.55	0.87
5q11.2	rs1353747	T/G	0.92 (0.79-1.06)	0.24	0.96 (0.93-0.99)	0.59	0.83	0.95 (0.92-0.98)	0.69	0.86	0.98 (0.92-1.03)	0.45	0.78
5q14.2	rs7707921	A/T	1.05 (0.95-1.17)	0.34	0.96 (0.94-0.98)	0.09	0.38	0.95 (0.93-0.97)	0.06	0.33	0.97 (0.93-1.00)	0.15	0.55
5q14.39	rs10474352	C/T	0.93 (0.83-1.06)	0.29	0.94 (0.92-0.97)	0.86	0.91	0.94 (0.91-0.96)	0.86	0.91	0.98 (0.94-1.03)	0.4	0.77
5q22.1	rs6882649	T/G	0.92 (0.83-1.01)	0.08	0.97 (0.95-0.99)	0.32	0.66	0.97 (0.95-0.99)	0.32	0.68	0.98 (0.94-1.01)	0.26	0.66
5q31.1	rs6596100	C/T	0.86 (0.77-0.96)	5.29E-03	0.94 (0.92-0.96)	0.12	0.41	0.94 (0.92-0.96)	0.12	0.45	0.95 (0.92-0.99)	0.09	0.43
5q33.3	rs1432679	T/C	0.95 (0.87-1.04)	0.25	1.08 (1.06-1.10)	0.01	0.1	1.07 (1.05-1.10)	9.56E-03	0.12	1.08 (1.04-1.11)	8.64E-03	0.09
5q35.1	rs4562056	G/T	0.95 (0.87-1.04)	0.29	1.05 (1.03-1.07)	0.03	0.21	1.06 (1.03-1.08)	0.02	0.17	1.02 (0.99-1.05)	0.13	0.55
6p25.3	rs11242675	T/C	0.98 (0.89-1.07)	0.66	1.00 (0.98-1.02)	0.69	0.86	1.00 (0.98-1.02)	0.69	0.86	0.99 (0.96-1.02)	0.84	0.94
6p24.3	rs9348512	C/A	1.08 (0.98-1.18)	0.12	1.00 (0.99-1.02)	0.12	0.41	1.00 (0.98-1.03)	0.13	0.45	1.01 (0.98-1.05)	0.2	0.6
6p23	rs204247	A/G	0.99 (0.91-1.09)	0.9	1.04 (1.02-1.06)	0.26	0.6	1.04 (1.02-1.06)	0.26	0.6	1.00 (0.97-1.03)	0.83	0.94
6p22.3	rs3819405	C/T	0.89 (0.81-0.98)	0.02	0.96 (0.94-0.97)	0.12	0.41	0.95 (0.93-0.97)	0.19	0.48	0.97 (0.94-1.00)	0.09	0.43
6p22.3	rs2223621	C/T	1.04 (0.95-1.14)	0.36	1.04 (1.02-1.06)	1	1	1.03 (1.01-1.06)	0.84	0.91	1.02 (0.99-1.05)	0.69	0.88
6p22.2	rs71557345	G/A	0.93 (0.80-1.09)	0.36	0.92 (0.88-0.96)	0.89	0.93	0.91 (0.87-0.96)	0.79	0.91	0.91 (0.84-0.98)	0.8	0.94

					Overall FBC			ER+ FBC			ER- FBC		
Cytoband	**SNP**	**Alleles**	**OR MBC**	***P* MBC**	**OR FBC[a]**	***P* Diff[b]**	***P* FDR**	**OR ER+[a]**	***P* Diff[b]**	***P* FDR**	**OR ER-[a]**	***P* Diff[b]**	***P* FDR**
6p22.1	rs9257408	G/C	1.06 (0.97-1.16)	0.21	1.02 (1.00-1.04)	0.41	0.72	1.03 (1.02-1.05)	0.55	0.77	1.04 (1.02-1.07)	0.7	0.88
6q14.1	rs12207986	A/G	1.03 (0.94-1.13)	0.49	0.97 (0.95-0.98)	0.21	0.55	0.97 (0.95-0.99)	0.21	0.53	0.96 (0.93-0.99)	0.15	0.55
6q14.1	rs17529111	T/C	1.14 (1.02-1.27)	0.02	1.02 (1.00-1.04)	0.05	0.31	1.01 (0.98-1.03)	0.04	0.27	1.06 (1.02-1.10)	0.23	0.64
6q23.1	rs6569648	T/C	0.99 (0.89-1.10)	0.81	0.94 (0.92-0.96)	0.35	0.7	0.95 (0.92-0.97)	0.47	0.76	0.94 (0.91-0.98)	0.36	0.77
6q25.19	rs9485372	G/A	1.04 (0.93-1.17)	0.48	0.96 (0.93-0.98)	0.18	0.52	0.95 (0.92-0.97)	0.13	0.45	0.99 (0.95-1.03)	0.42	0.77
6q25	rs3757322	T/G	1.23 (1.12-1.35)	1.11E-05	1.08 (1.06-1.10)	0.01	0.1	1.06 (1.04-1.08)	2.29E-03	0.05	1.14 (1.10-1.18)	0.14	0.55
6q25	rs9397437	G/A	1.58 (1.34-1.87)	4.22E-08	1.17 (1.14-1.21)	4.15E-04	0.03	1.14 (1.10-1.18)	1.48E-04	9.52E-03	1.32 (1.25-1.4)	0.04	0.28
6q25	rs2747652	C/T	0.87 (0.80-0.95)	2.72E-03	0.94 (0.92-0.96)	0.08	0.38	0.95 (0.93-0.97)	0.05	0.31	0.92 (0.89-0.95)	0.22	0.64
7p15.3	rs7971	A/G	0.97 (0.88-1.06)	0.46	0.96 (0.94-0.98)	0.84	0.91	0.96 (0.94-0.98)	0.84	0.91	0.96 (0.93-0.99)	0.84	0.94
7p15.1	rs17156577	T/C	1.01 (0.88-1.17)	0.85	1.05 (1.02-1.08)	0.59	0.83	1.05 (1.02-1.08)	0.59	0.8	1.05 (1.00-1.10)	0.6	0.88
7q21.2	rs6964587	G/T	1.02 (0.93-1.11)	0.72	1.03 (1.02-1.05)	0.84	0.91	1.03 (1.01-1.05)	0.84	0.91	1.02 (0.98-1.05)	1	1
7q21.3	rs17268829	T/C	1.04 (0.94-1.14)	0.45	1.05 (1.03-1.07)	0.86	0.91	1.06 (1.04-1.08)	0.72	0.88	1.02 (0.98-1.05)	0.73	0.89
7q22.1	rs71559437	G/A	1.02 (0.90-1.16)	0.76	0.93 (0.91-0.96)	0.15	0.47	0.92 (0.89-0.95)	0.12	0.45	0.95 (0.90-1.00)	0.31	0.7
7q32.3	rs4593472	C/T	0.95 (0.87-1.05)	0.32	0.97 (0.95-0.99)	0.65	0.86	0.97 (0.95-0.99)	0.65	0.86	0.97 (0.93-1.00)	0.68	0.88
7q34	rs11977670	G/A	1.04 (0.95-1.14)	0.37	1.06 (1.04-1.08)	0.69	0.86	1.06 (1.04-1.09)	0.69	0.86	1.02 (0.99-1.05)	0.69	0.88
7q35	rs720475	G/A	1.05 (0.95-1.17)	0.32	0.96 (0.94-0.98)	0.09	0.38	0.96 (0.94-0.98)	0.09	0.39	1.00 (0.96-1.03)	0.38	0.77
8p12	rs9693444	C/A	1.08 (0.98-1.18)	0.13	1.06 (1.04-1.08)	0.71	0.87	1.07 (1.05-1.10)	0.85	0.91	1.02 (0.98-1.05)	0.29	0.67
8p11.23	rs13365225	A/G	1.02 (0.90-1.15)	0.81	0.91 (0.89-0.93)	0.08	0.38	0.91 (0.89-0.94)	0.08	0.39	0.90 (0.86-0.94)	0.07	0.36
8q21.11	rs6472903	T/G	0.94 (0.84-1.05)	0.29	0.94 (0.92-0.96)	1	1	0.93 (0.91-0.96)	0.85	0.91	0.96 (0.92-1.00)	0.73	0.89
8q21.11	rs2943559	A/G	1.19 (1.01-1.40)	0.04	1.10 (1.07-1.14)	0.35	0.7	1.10 (1.06-1.14)	0.36	0.72	1.10 (1.04-1.16)	0.37	0.77
8q22.3	rs514192	T/A	1.16 (1.06-1.28)	2.29E-03	1.05 (1.03-1.07)	0.03	0.21	1.06 (1.03-1.08)	0.06	0.34	1.01 (0.98-1.05)	4.30E-03	0.05
8q23.1	rs12546444	A/T	0.89 (0.76-1.03)	0.12	0.93 (0.91-0.96)	0.59	0.83	0.93 (0.89-0.96)	0.6	0.81	0.98 (0.93-1.03)	0.26	0.66
8q23.3	rs13267382	G/A	1.02 (0.92-1.12)	0.74	1.03 (1.01-1.05)	0.86	0.91	1.04 (1.01-1.06)	0.72	0.88	1.02 (0.98-1.05)	1	1
8q24.13	rs58847541	G/A	1.18 (1.04-1.33)	0.01	1.08 (1.05-1.10)	0.18	0.52	1.07 (1.04-1.10)	0.14	0.46	1.13 (1.08-1.18)	0.53	0.87
8q24.21	rs13281615	A/G	1.06 (0.97-1.16)	0.21	1.11 (1.09-1.13)	0.32	0.66	1.11 (1.09-1.14)	0.32	0.68	1.07 (1.03-1.10)	0.85	0.94
8q24.21	rs11780156	C/T	1.07 (0.95-1.20)	0.26	1.05 (1.03-1.08)	0.76	0.91	1.05 (1.02-1.08)	0.76	0.91	1.05 (1.01-1.10)	0.77	0.92
9p21.3	rs1011970	G/T	1.11 (0.99-1.25)	0.08	1.07 (1.04-1.09)	0.54	0.8	1.06 (1.04-1.09)	0.44	0.73	1.05 (1.00-1.09)	0.38	0.77
9q31.2	rs10759243	C/A	0.95 (0.86-1.05)	0.31	1.06 (1.04-1.08)	0.03	0.21	1.07 (1.05-1.10)	0.02	0.17	1.02 (0.99-1.06)	0.18	0.59
9q31.2	rs10816625	A/G	0.85 (0.71-1.03)	0.09	1.11 (1.07-1.15)	4.40E-03	0.09	1.13 (1.08-1.17)	2.64E-03	0.05	1.07 (1.01-1.14)	0.02	0.13
9q31.2	rs13294895	C/T	0.96 (0.85-1.08)	0.52	1.06 (1.03-1.08)	0.12	0.41	1.07 (1.05-1.10)	0.08	0.39	0.99 (0.95-1.04)	0.64	0.88
9q31.2	rs676256	T/C	1.01 (0.92-1.11)	0.8	0.91 (0.90-0.93)	0.03	0.21	0.90 (0.88-0.92)	0.02	0.16	0.98 (0.94-1.01)	0.56	0.88
9q33.1	rs1895062	A/G	1.07 (0.98-1.17)	0.16	0.94 (0.92-0.95)	0.01	0.1	0.94 (0.92-0.96)	5.00E-03	0.07	0.93 (0.90-0.96)	3.38E-03	0.05
9q33.3	rs10760444	A/G	0.99 (0.90-1.08)	0.78	1.03 (1.02-1.05)	0.42	0.72	1.03 (1.01-1.05)	0.42	0.72	1.05 (1.02-1.08)	0.25	0.64
9q34.2	rs8176636	I*/T	0.98 (0.87-1.09)	0.66	1.03 (1.01-1.06)	0.42	0.72	1.04 (1.01-1.06)	0.34	0.7	1.05 (1.01-1.09)	0.28	0.67
10p15.1	rs2380205	C/T	1.01 (0.92-1.10)	0.89	0.98 (0.96-0.99)	0.54	0.8	0.98 (0.96-1.00)	0.54	0.77	0.97 (0.94-1.00)	0.42	0.77
10p14	rs67958007	TG/T	1.04 (0.91-1.19)	0.56	1.09 (1.06-1.12)	0.5	0.8	1.09 (1.06-1.12)	0.5	0.77	1.08 (1.03-1.14)	0.6	0.88
10p12.31	rs7072776	G/A	1.17 (1.06-1.29)	1.60E-03	1.05 (1.03-1.07)	0.03	0.21	1.07 (1.04-1.09)	0.09	0.39	0.99 (0.95-1.02)	2.21E-03	0.03
10p12.31	rs11814448	A/C	0.84 (0.60-1.19)	0.32	1.12 (1.06-1.19)	0.1	0.41	1.15 (1.07-1.22)	0.07	0.38	1.04 (0.94-1.16)	0.23	0.64

					Overall FBC			ER+ FBC			ER- FBC		
Cytoband	**SNP**	**Alleles**	**OR MBC**	***P* MBC**	**OR FBC[a]**	***P* Diff[b]**	***P* FDR**	**OR ER+[a]**	***P* Diff[b]**	***P* FDR**	**OR ER-[a]**	***P* Diff[b]**	***P* FDR**
10q21.2	rs10995201	A/G	0.85 (0.75-0.96)	0.01	0.90 (0.88-0.92)	0.38	0.72	0.89 (0.87-0.92)	0.48	0.76	0.93 (0.89-0.98)	0.18	0.59
10q22.3	rs704010	C/T	1.04 (0.95-1.14)	0.42	1.07 (1.05-1.09)	0.55	0.8	1.08 (1.06-1.10)	0.42	0.72	1.06 (1.03-1.09)	0.69	0.88
10q23.33	rs140936696	C/CAA	1.01 (0.90-1.13)	0.86	1.04 (1.02-1.07)	0.62	0.85	1.05 (1.02-1.07)	0.52	0.77	1.04 (0.99-1.08)	0.65	0.88
10q25.2	rs7904519	A/G	1.02 (0.94-1.12)	0.61	1.03 (1.01-1.05)	0.82	0.91	1.02 (1.00-1.04)	1	1	1.08 (1.04-1.11)	0.21	0.63
10q26.12	rs11199914	C/T	0.94 (0.86-1.04)	0.25	0.96 (0.94-0.98)	0.65	0.86	0.95 (0.93-0.97)	0.82	0.91	0.98 (0.95-1.02)	0.39	0.77
10q26.13	rs2981578	T/C	1.08 (0.99-1.18)	0.07	1.23 (1.21-1.25)	3.99E-03	0.09	1.28 (1.26-1.31)	1.66E-04	9.52E-03	1.04 (1.00-1.07)	0.44	0.77
10q26.13	rs35054928	G/GC	1.13 (1.03-1.23)	8.65E-03	1.27 (1.25-1.30)	0.01	0.1	1.34 (1.31-1.37)	4.61E-04	0.02	1.06 (1.03-1.10)	0.2	0.6
10q26.13	rs45631563	A/T	0.81 (0.65-1.00)	0.05	0.81 (0.78-0.85)	1	1	0.77 (0.73-0.81)	0.66	0.86	0.93 (0.86-1.00)	0.25	0.64
11p15	rs6597981	G/A	1.04 (0.95-1.14)	0.39	0.96 (0.94-0.97)	0.09	0.38	0.96 (0.94-0.98)	0.09	0.39	0.94 (0.91-0.97)	0.04	0.27
11p15.5	rs3817198	T/C	1.07 (0.98-1.18)	0.15	1.05 (1.03-1.07)	0.68	0.86	1.05 (1.03-1.08)	0.68	0.86	1.02 (0.99-1.06)	0.31	0.7
11q13.1	rs3903072	G/T	1.03 (0.94-1.12)	0.55	0.97 (0.95-0.99)	0.21	0.55	0.96 (0.94-0.98)	0.14	0.46	0.99 (0.96-1.02)	0.42	0.77
11q13.3	rs554219	C/G	1.42 (1.24-1.62)	1.86E-07	1.21 (1.18-1.24)	0.02	0.17	1.27 (1.24-1.31)	0.11	0.45	0.98 (0.94-1.03)	2.96E-07	2.55E-05
11q13.3	rs75915166	C/A	1.52 (1.25-1.83)	1.64E-05	1.28 (1.24-1.33)	0.09	0.38	1.35 (1.29-1.40)	0.25	0.59	0.99 (0.92-1.06)	5.73E-05	2.47E-03
11q24.3	rs11820646	C/T	1.01 (0.92-1.11)	0.81	0.96 (0.94-0.98)	0.3	0.65	0.97 (0.95-0.99)	0.41	0.72	0.94 (0.91-0.97)	0.15	0.55
12p13.1	rs12422552	G/C	1.05 (0.95-1.16)	0.33	1.06 (1.04-1.08)	0.86	0.91	1.05 (1.03-1.07)	1	1	1.04 (1.01-1.08)	0.86	0.94
12p11.22	rs7297051	C/T	0.87 (0.78-0.97)	9.71E-03	0.89 (0.87-0.91)	0.69	0.86	0.90 (0.87-0.92)	0.56	0.78	0.87 (0.84-0.91)	1	1
12q21.31	rs202049448	T/C	0.96 (0.87-1.06)	0.44	0.95 (0.93-0.97)	0.84	0.91	0.95 (0.93-0.97)	0.84	0.91	0.93 (0.90-0.96)	0.55	0.87
12q22	rs17356907	A/G	0.96 (0.87-1.06)	0.4	0.91 (0.90-0.93)	0.29	0.65	0.92 (0.90-0.94)	0.41	0.72	0.94 (0.91-0.97)	0.69	0.88
12q24.21	rs1292011	A/G	0.97 (0.89-1.06)	0.46	0.92 (0.90-0.94)	0.24	0.59	0.91 (0.89-0.92)	0.16	0.48	0.98 (0.95-1.01)	0.83	0.94
12q24.31	rs206966	C/T	0.97 (0.86-1.1)	0.69	1.05 (1.02-1.07)	0.21	0.55	1.06 (1.03-1.09)	0.16	0.48	1.04 (1.00-1.09)	0.28	0.67
13q13.1	rs11571833	A/T	1.82 (1.18-2.81)	6.70E-03	1.35 (1.23-1.48)	0.19	0.53	1.28 (1.15-1.42)	0.12	0.45	1.58 (1.35-1.84)	0.55	0.87
13q22.1	rs6562760	G/A	1.01 (0.91-1.12)	0.88	0.95 (0.93-0.97)	0.26	0.6	0.95 (0.93-0.98)	0.26	0.59	0.92 (0.88-0.95)	0.11	0.46
14q13.3	rs2236007	G/A	0.97 (0.88-1.09)	0.64	0.93 (0.91-0.95)	0.41	0.72	0.93 (0.91-0.96)	0.41	0.72	0.95 (0.91-0.99)	0.7	0.88
14q24.1	rs2588809	C/T	1.59 (1.41-1.78)	4.58E-15	1.06 (1.03-1.08)	1.25E-10	2.15E-08	1.07 (1.04-1.10)	3.22E-10	5.55E-08	0.99 (0.95-1.03)	2.67E-13	4.58E-11
14q24.1	rs999737	C/T	0.88 (0.79-0.97)	0.01	0.91 (0.89-0.93)	0.55	0.8	0.91 (0.88-0.93)	0.56	0.78	0.92 (0.89-0.96)	0.44	0.77
14q32.11	rs941764	A/G	1.05 (0.96-1.15)	0.28	1.03 (1.02-1.05)	0.68	0.86	1.03 (1.01-1.06)	0.68	0.86	1.01 (0.98-1.04)	0.42	0.77
14q32.12	rs11627032	T/C	0.92 (0.84-1.02)	0.12	0.96 (0.94-0.98)	0.37	0.72	0.96 (0.94-0.98)	0.37	0.72	0.95 (0.92-0.99)	0.51	0.86
14q32.33	rs10623258	C/CTT	1.11 (1.02-1.22)	0.02	1.04 (1.02-1.06)	0.14	0.45	1.04 (1.02-1.06)	0.14	0.46	1.03 (1.00-1.06)	0.1	0.45
15q26.19	rs2290203	G/A	0.93 (0.83-1.04)	0.2	0.94 (0.92-0.96)	0.86	0.91	0.94 (0.91-0.96)	0.86	0.91	0.96 (0.92-1.00)	0.61	0.88
16q12.1	rs4784227	C/T	1.40 (1.27-1.54)	4.49E-11	1.23 (1.20-1.25)	0.01	0.1	1.25 (1.22-1.28)	0.03	0.19	1.14 (1.10-1.19)	1.05E-04	3.00E-03
16q12.2	rs17817449	T/G	1.04 (0.95-1.14)	0.37	0.95 (0.93-0.96)	0.06	0.34	0.95 (0.93-0.97)	0.06	0.33	0.93 (0.90-0.96)	0.02	0.16
16q12.2	rs11075995	T/A	1.02 (0.92-1.13)	0.7	1.03 (1.01-1.06)	0.86	0.91	1.02 (0.99-1.04)	1	1	1.07 (1.03-1.11)	0.39	0.77
16q12.2	rs28539243	G/A	1.04 (0.95-1.13)	0.44	1.05 (1.03-1.07)	0.84	0.91	1.05 (1.03-1.07)	0.84	0.91	1.05 (1.01-1.08)	0.85	0.94
16q13	rs2432539	G/A	1.07 (0.98-1.17)	0.12	1.03 (1.02-1.05)	0.4	0.72	1.04 (1.02-1.06)	0.54	0.77	1.02 (0.99-1.06)	0.31	0.7
16q23.2	rs13329835	A/G	1.05 (0.95-1.17)	0.36	1.07 (1.05-1.09)	0.72	0.88	1.08 (1.05-1.11)	0.6	0.81	1.06 (1.02-1.10)	0.86	0.94
16q24.2	rs4496150	C/A	1.02 (0.92-1.14)	0.64	0.96 (0.94-0.98)	0.26	0.6	0.96 (0.94-0.99)	0.26	0.59	0.96 (0.92-0.99)	0.29	0.67
17q11.2	rs146699004	GGT/G	0.92 (0.83-1.02)	0.1	0.97 (0.95-0.99)	0.32	0.66	0.96 (0.94-0.99)	0.43	0.72	0.96 (0.93-0.98)	0.44	0.77
17q21.2	rs72826962	C/T	1.22 (0.82-1.82)	0.32	1.20 (1.11-1.30)	0.94	0.97	1.20 (1.10-1.31)	0.94	0.96	1.13 (0.98-1.30)	0.72	0.89

					Overall FBC			ER+ FBC			ER- FBC		
Cytoband	**SNP**	**Alleles**	**OR MBC**	***P* MBC**	**OR FBC[a]**	***P* Diff[b]**	***P* FDR**	**OR ER+[a]**	***P* Diff[b]**	***P* FDR**	**OR ER-[a]**	***P* Diff[b]**	***P* FDR**
17q21.31	rs2532263	G/A	1.00 (0.89-1.12)	0.97	0.95 (0.93-0.97)	0.4	0.72	0.95 (0.93-0.98)	0.4	0.72	0.95 (0.91-0.99)	0.42	0.77
17q22	rs2787486	A/C	0.98 (0.89-1.08)	0.73	0.93 (0.91-0.94)	0.3	0.65	0.91 (0.89-0.93)	0.14	0.46	0.96 (0.93-1.00)	0.69	0.88
17q25.3	rs745570	G/A	1.00 (0.92-1.10)	0.95	1.03 (1.01-1.05)	0.5	0.8	1.02 (1.00-1.04)	0.65	0.86	1.04 (1.01-1.07)	0.38	0.77
18q11.2	rs527616	G/C	0.95 (0.86-1.04)	0.27	0.97 (0.95-0.98)	0.69	0.86	0.95 (0.94-0.97)	1	1	1.00 (0.97-1.03)	0.33	0.73
18q11.2	rs1436904	T/G	1.02 (0.94-1.12)	0.58	0.95 (0.94-0.97)	0.09	0.38	0.94 (0.92-0.96)	0.06	0.33	0.99 (0.96-1.03)	0.5	0.85
18q12.1	rs117618124	T/C	0.88 (0.71-1.09)	0.25	0.89 (0.85-0.92)	0.92	0.96	0.89 (0.85-0.94)	0.92	0.95	0.84 (0.77-0.91)	0.69	0.88
18q12.3	rs6507583	A/G	0.82 (0.69-0.97)	0.02	0.92 (0.89-0.96)	0.2	0.55	0.90 (0.86-0.94)	0.31	0.67	0.97 (0.91-1.03)	0.07	0.38
19p13.13	rs78269692	T/C	1.18 (0.97-1.44)	0.09	1.09 (1.04-1.13)	0.44	0.73	1.09 (1.04-1.14)	0.44	0.73	1.09 (1.02-1.17)	0.45	0.78
19p13.12	rs2594714	G/A	0.90 (0.81-1.00)	0.06	0.97 (0.95-0.99)	0.17	0.5	0.97 (0.95-1.00)	0.17	0.48	1.00 (0.96-1.04)	0.07	0.36
19p13.11	rs67397200	C/G	1.02 (0.93-1.13)	0.62	1.03 (1.01-1.05)	0.84	0.91	0.99 (0.97-1.01)	0.54	0.77	1.17 (1.13-1.21)	6.44E-03	0.07
19p13.11	rs4808801	A/G	0.95 (0.86-1.04)	0.23	0.93 (0.91-0.95)	0.68	0.86	0.92 (0.91-0.94)	0.53	0.77	0.96 (0.93-0.99)	0.84	0.94
19p13.11	rs2965183	G/A	0.98 (0.89-1.07)	0.66	1.04 (1.02-1.06)	0.24	0.59	1.04 (1.02-1.06)	0.24	0.58	1.05 (1.02-1.09)	0.18	0.59
19q13.31	rs3760982	G/A	1.02 (0.93-1.11)	0.72	1.05 (1.03-1.07)	0.55	0.8	1.06 (1.04-1.08)	0.42	0.72	1.08 (1.05-1.12)	0.25	0.64
19q13.22	rs71338792	A/AT	0.92 (0.83-1.03)	0.17	1.05 (1.03-1.07)	0.01	0.1	1.05 (1.03-1.08)	0.01	0.13	1.03 (0.99-1.07)	0.04	0.29
20p12.3	rs16991615	G/A	1.02 (0.85-1.21)	0.86	1.10 (1.06-1.14)	0.43	0.73	1.10 (1.06-1.14)	0.43	0.72	1.10 (1.04-1.18)	0.44	0.77
20q11.22	rs2284378	C/T	1.13 (1.03-1.24)	0.01	1.00 (0.98-1.02)	0.01	0.1	1.00 (0.97-1.02)	0.01	0.13	0.99 (0.95-1.02)	0.01	0.1
20q13.13	rs6122906	A/G	1.09 (0.96-1.22)	0.18	1.05 (1.03-1.07)	0.57	0.82	1.04 (1.02-1.07)	0.47	0.76	1.08 (1.03-1.12)	0.89	0.96
21q21.1	rs2823093	G/A	1.00 (0.90-1.11)	1	0.94 (0.92-0.96)	0.26	0.6	0.92 (0.91-0.94)	0.12	0.45	1.00 (0.96-1.04)	1	1
22q12.1	rs17879961	A/G	0.88 (0.24-3.23)	0.85	1.26 (1.11-1.42)	0.59	0.83	1.39 (1.22-1.60)	0.49	0.77	0.86 (0.68-1.09)	0.97	1
22q12.2	rs132390	T/C	1.42 (1.11-1.82)	4.71E-03	1.04 (0.99-1.09)	0.02	0.17	1.04 (0.98-1.09)	0.02	0.14	1.01 (0.92-1.09)	0.01	0.1
22q13.1	rs738321	C/G	0.99 (0.90-1.08)	0.78	0.95 (0.93-0.97)	0.41	0.72	0.93 (0.91-0.95)	0.21	0.53	0.99 (0.96-1.02)	1	1
22q13.19	chr22:39359355	I/D	1.10 (0.93-1.30)	0.28	1.10 (1.07-1.14)	1	1	1.11 (1.07-1.15)	0.92	0.95	1.09 (1.04-1.14)	0.92	0.97
22q13.1	rs6001930	T/C	1.16 (1.00-1.34)	0.05	1.12 (1.09-1.16)	0.65	0.86	1.11 (1.08-1.15)	0.57	0.78	1.14 (1.08-1.19)	0.83	0.94
22q13.2	rs73161324	C/T	1.16 (0.95-1.43)	0.15	1.06 (1.02-1.09)	0.38	0.72	1.04 (1.00-1.08)	0.29	0.65	1.10 (1.03-1.18)	0.62	0.88
22q13.31	rs28512361	G/A	0.93 (0.80-1.08)	0.34	1.05 (1.02-1.08)	0.12	0.41	1.05 (1.02-1.08)	0.12	0.45	1.09 (1.04-1.14)	0.05	0.3

[a] Effect estimates obtained from Michailidou et al. Nature 2017;551(7678):92-94. (8)

[b] *P*-value for the significance of the differences between the MBC and FBC ORs.

Supplementary Table 7: Conditional analyses of SNPs at 6q25.1, 10p12.31 and 11q13.3.

Cytoband	Conditioning SNP	SNP	Alleles	MAF	Score X2	P-value
6q25.1	**rs9397437**	rs3757322	T|G	0.327|0.377	14.05	1.78×10^{-04}
		rs9383938	G|T	0.079|0.111	2.51	0.11
	rs3757322	rs9397437	G|A	0.070|0.099	12.04	5.22×10^{-04}
		rs9383938	G|T	0.080|0.112	15	1.08×10^{-04}
	rs9383938	rs3757322	T|G	0.328|0.379	16.27	5.49×10^{-05}
		rs9397437	G|A	0.070|0.099	0.52	0.47
10p12.31	**rs7072776**	rs2183271	T|C	0.359|0.409	12	5.33×10^{-04}
	rs2183271	rs7072776	G|A	0.274|0.305	0.98	0.32
11q13.3	**rs78540526**	rs75915166	C|A	0.051|0.073	0.22	0.64
		rs554219	C|G	0.114|0.153	4.78	0.03
	rs75915166	rs78540526	C|T	0.064|0.096	16.25	5.55×10^{-05}
		rs554219	C|G	0.115|0.155	16.55	4.74×10^{-05}
	rs554219	rs78540526	C|T	0.066|0.098	6.44	0.01
		rs75915166	C|A	0.051|0.074	2.17	0.14

Supplementary Figures

Supplementary Figure 1: GWAS design and data quality control. Sources and numbers of case and control subjects contributing to each GWAS dataset are indicated in the top row of the figure, as are the SNP genotyping arrays which were used for genome-wide genotyping. Sample and SNP exclusions are indicated alongside the reason for their exclusion. The total number of directly genotyped SNPs harmonised in cases and controls prior to 1KGP imputation is shown in the middle row.

Supplementary Figure 2: QQ plots of association statistics. The distributions of the observed vs. expected *P*-values from 1,028 MBC cases (UK-BCN-MBCS, UK-UoC, UK-UoL, US-CoH) genotyped using Illumina Infinium OmniExpress and 2,664 controls (UK-58BC, UK-BCN-MBCS) that had been genotyped using Illumina 1.2M Duo arrays (**A**), 191 cases (UK-BCN-MBCS) and 704 controls (UK-GS, UK-BCN-MBCS) genotyped using the Illumina Infinium Oncoarray (**B**) and 161 cases and 252 controls (UK-BCN-MBCS) genotyped using the Illumina Infinium Global Screening Array (**C**). Test statistic inflation (red line) was assessed using lambda statistics and the null distribution is indicated by the solid black line.

Supplementary Figure 3: Manhattan plot of meta-analysed association data. $-\log_{10}$ *P*-values for association with predisposition to MBC of 8,074,073 autosomal SNPs.

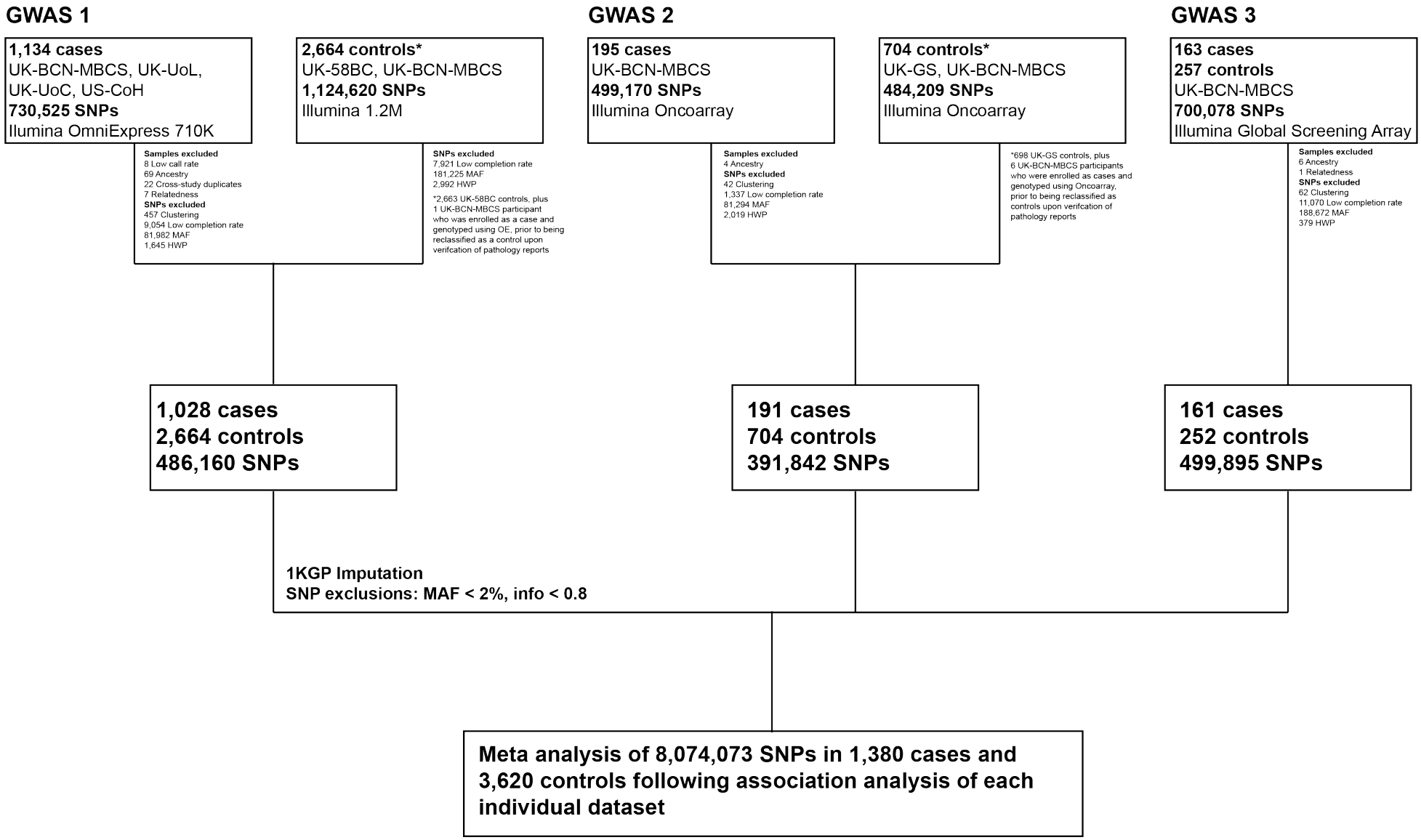
Supplementary Figure 4: Forest plots for the loci subject to replication analysis. Forest plots and individual effect estimates, p-values and p-values for heterogeneity for each study that contributed to the replication dataset.

Supplementary Figure 5: Gene expression of candidate gene targets in normal male (n = 157) and female (n = 107) breast tissue samples. Boxes represent median, 25th and 75th percentiles of normalised gene count, whiskers indicate the lowest and highest values with 1.5 IQR of the lower and upper quartiles. Outliers are plotted as circles. *P*-values were calculated using linear regression.

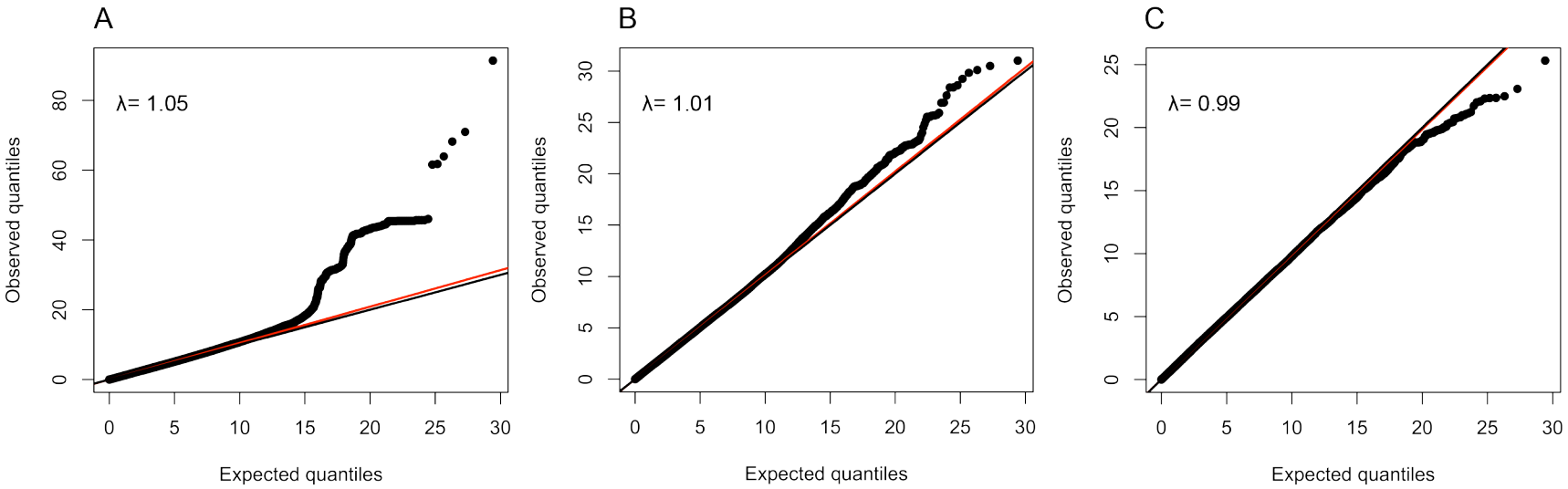
Supplementary Figure 6: Box plots of eQTL analysis between predisposition SNPs and putative target genes in normal breast tissue (n = 264). For SNPs that had homozygote genotype counts < 10, analyses were performed on two genotype groups. Numbers of individuals with each given genotype are indicated on the x-axis. Boxes represent median, 25th and 75th percentiles of normalised gene count, whiskers indicate the lowest and highest values with 1.5 IQR of the lower and upper quartiles. Outliers are plotted as circles.

Supplementary Figure 7: Interaction analysis of genotype and sex on gene expression. Numbers of individuals with each given genotype are indicated on the x-axis.

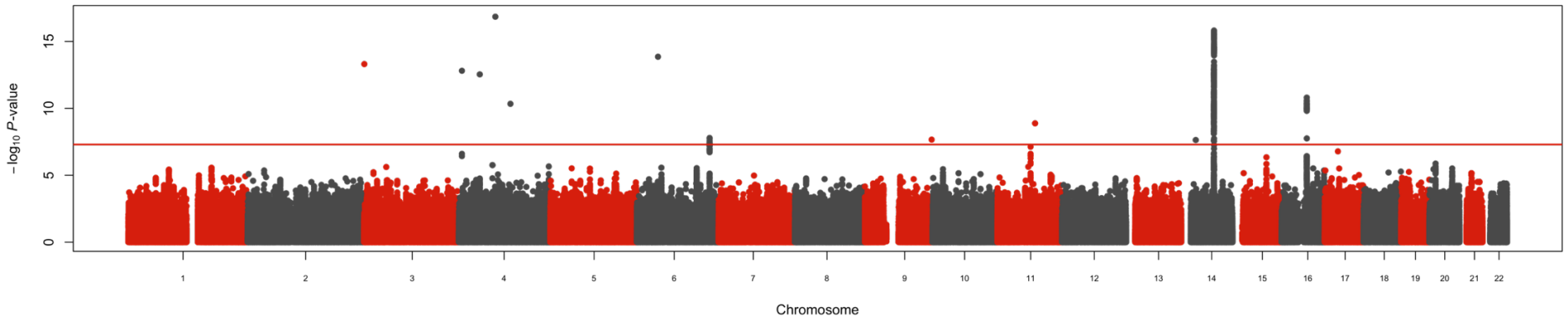
Supplementary Figure 1: GWAS design and data quality control.



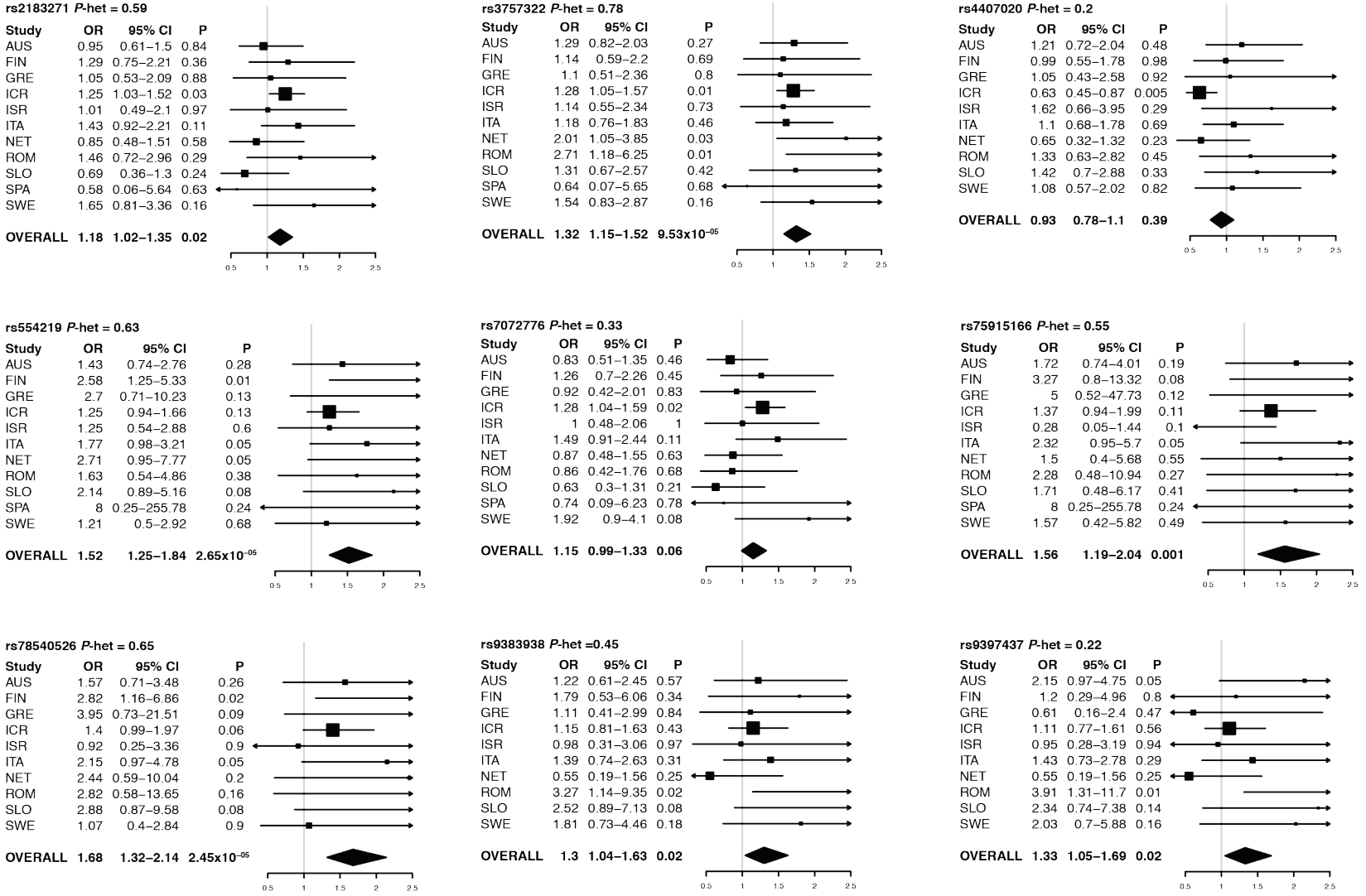
Supplementary Figure 2: QQ plots of association statistics.



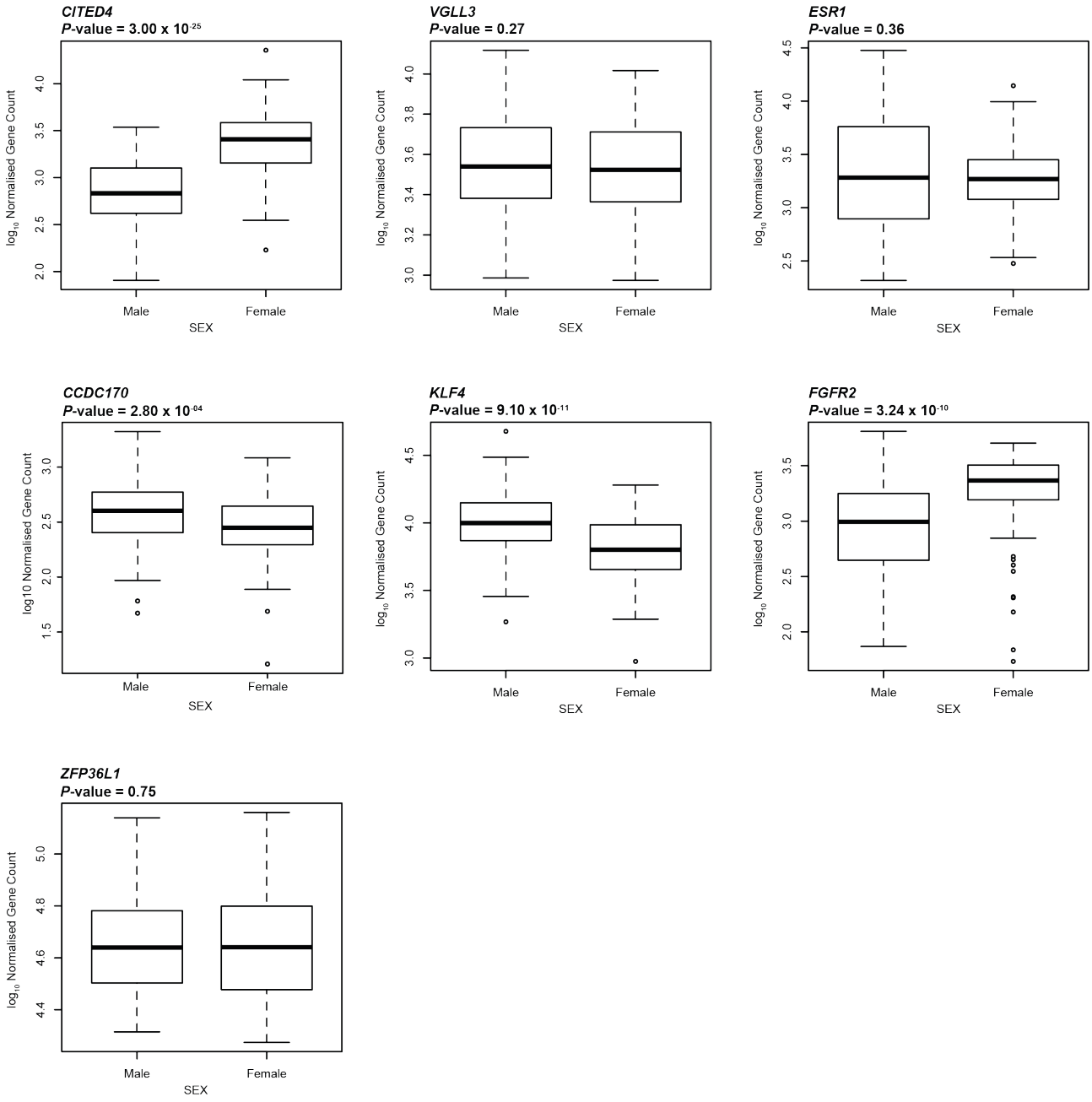
Supplementary Figure 3: Manhattan plot of meta-analysed MBC GWAS data.



Supplementary Figure 4: Individual effect estimates for SNPs genotyped in replication analysis.



Supplementary Figure 5: Gene expression of candidate target genes in normal male (n = 157) and female (n = 107) breast tissue samples.



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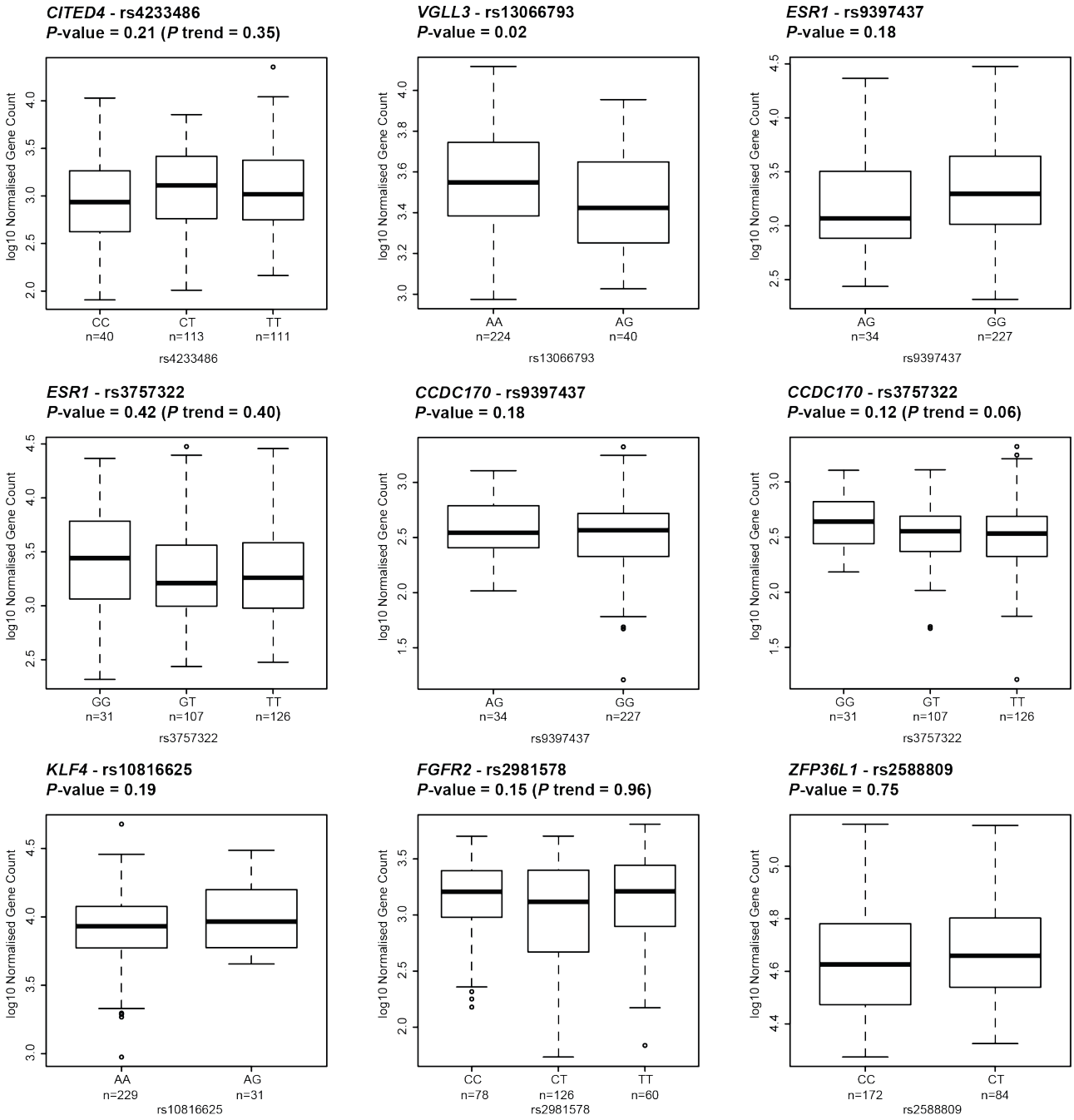
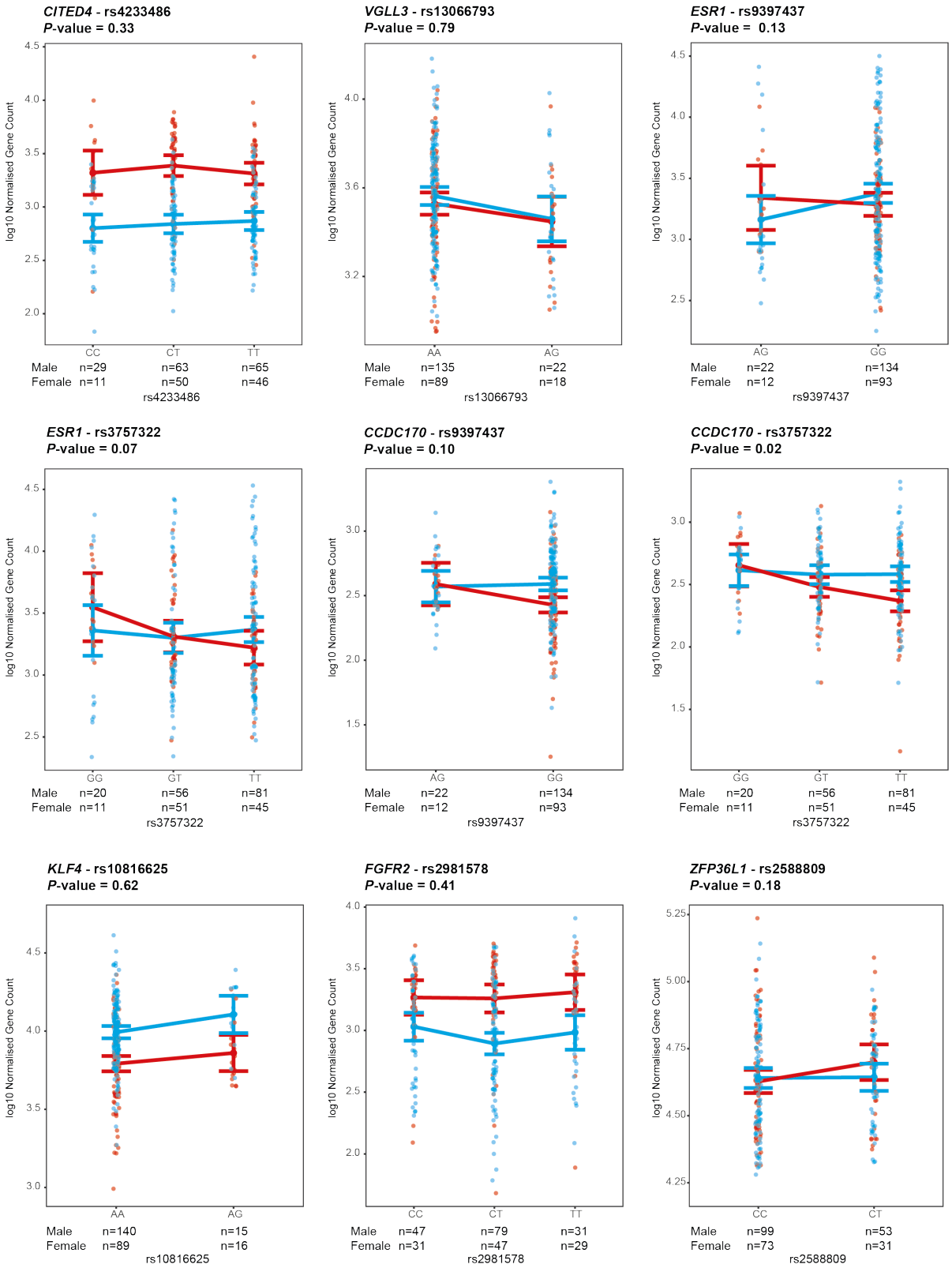
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