**Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer**

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**Genome wide association studies (GWAS) and large scale replication studies have identified common variants in 79 loci associated with breast cancer, explaining ~14% of the familial risk of the disease. To identify new susceptibility loci, we performed a meta-analysis of 11 GWAS comprising of 15,748 breast cancer cases and 18,084 controls, and 46,785 cases and 42,892 controls from 41 studies genotyped on a 200K custom array (iCOGS). Analyses were restricted to women of European ancestry. Genotypes for more than 11M SNPs were generated by imputation using the 1000 Genomes Project reference panel. We identified 15 novel loci associated with breast cancer at $P<5x10^{-8}$. Combining association analysis with ChIP-Seq data in mammary cell lines and ChIA-PET chromatin interaction data in ENCODE, we identified likely target genes in two regions: *SETBP1* on 18q12.3 and *RNF115* and *PDZK1* on 1q21.1. One association appears to be driven by an amino-acid substitution in *EXO1*.**

Breast cancer is the most common cancer in women worldwide[1]. The disease aggregates in families, and has an important inherited component. This inherited component is driven by a combination of rare variants, notably in *BRCA1*, *BRCA2*, *PALB2, ATM* and *CHEK2* conferring a moderate or high lifetime risk of the disease, , together with common variants at more than 70 loci, identified through GWAS and large scale replication studies[2-20]. Taken together, these loci explain approximately one-third of the excess familial risk of breast cancer.

The majority of susceptibility SNPs has been identified through the Breast Cancer Association Consortium (BCAC), a collaboration involving more than 50 case-control studies. We recently reported the results of a large-scale genotyping experiment within BCAC, which utilised a custom array (iCOGS) designed to study variants of interest for breast, ovarian and prostate cancers. iCOGS comprised more than 200,000 variants, of which 29,807 had been selected from combined analysis of nine breast cancer GWAS involving 10,052 breast cancer cases and 12,575 controls of European ancestry. In total, 45,290 breast cancer cases and 41,880 controls of European ancestry from 41 studies were genotyped with iCOGS, leading to the discovery of 41 novel susceptibility loci[16]. A parallel analysis identified four loci specific to oestrogen receptor (ER)-negative disease[17] . However, additional susceptibility loci may have been missed because they were not selected from the original GWAS, or not included on the array.

Genotype imputation is a powerful approach to infer missing genotypes using the genetic correlations defined in a densely genotyped reference panel, thus providing the opportunity to identify novel susceptibility variants even if not directly genotyped[21]. In this analysis we aimed to

identify additional breast cancer susceptibility loci by utilising data from all 200k variants on the iCOGS array, and used imputation to estimate genotypes for more than 11M SNPs. We applied the same approach to data from 11 GWAS. After quality control (QC) exclusions, the dataset comprised 15,748 breast cancer cases and 18,084 controls from GWAS, and 46,785 cases and 42,892 controls from 41 studies genotyped with iCOGS (see Online Methods and Supplementary Tables 1a-1e). All subjects were women of European ancestry.

We imputed genotypes using the 1000 Genomes Project March 2012 release as the reference dataset (see Online Methods) The main analyses were based on ~11.6M SNPs that were imputed with imputation $r^2$ >0.3 and had MAF>0.005 in at least one of the datasets[22].

Of common SNPs (MAF>0.05), 88% were imputed from the iCOGS array with $r^2$>0.5; this compared to 99% of variants for the largest GWAS (UK2), which was genotyped using a 670k SNP array (Figure 1a and 1b, Supplementary Table 2). Thirty-seven per cent of common SNPs were imputed on the iCOGS with $r^2$>0.9 , compared with 85% for UK2. Thus, despite being designed as a follow-up of GWAS for different diseases rather than a genome-wide array, the majority of common variants could be imputed using the iCOGS, but the overall imputation quality was, poorer that from a standard GWAS array. Imputation quality decreased with decreasing allele frequency (Figure 1c and 1d, Supplementary Table 2).

Log odds ratio estimates and standard errors were calculated for each dataset using logistic regression, adjusting for principal components where it was found to reduce substantially the inflation factor. We then combined the results from each dataset for variants with MAF >0.5% using a fixed effects meta-analysis[23]. More than 7,000 variants with a combined $P<5\times10^{-8}$ for association were identified, the large majority of which was in regions previously shown to be associated with breast cancer susceptibility. Of the 79 previously published breast cancer susceptibility loci identified in women of European ancestry, all but eight show evidence of association at $P<5\times10^{-8}$ for overall, ER-positive or ER-negative disease risk (Supplementary Tables 3a, 3b and 3c). For four of the eight variants, (rs1550623 on 2q31, rs11571833 on 13q13.1, rs12422552 on 12p13.1 and rs11242674 on 6p25.3), slightly weaker evidence of association was observed. One reported variant, rs7726159 did not reach $P<5\times10^{-8}$ in this ($P$=0.0017) or the previous analysis – it was identified through fine-mapping of the *TERT* region on 5p15.33[18]. One other variant in *AKAP9,* rs6964587 reported previously[19] did not reach $P<5\times10^{-8}$ but an alternative correlated with it did ($P=3.67\times10^{-8}$ for chr7:91681597:D; $r^2$ between the two markers = 0.98). The two remaining variants (rs2380205 on 10p15 and rs1045485 at *CASP8*) were reported in earlier analysis[9,24] but did not even reach

*P*<0.0001, suggesting that they may have been false positive reports. An alternative variant at *CASP8*, rs1830298 ($r^2$=0.06, D'=1 with rs1045485 in 1000G CEU) did reach P<5x$10^{-8}$ in this dataset[25].

To assess evidence for additional susceptibility loci, we removed all SNPs within 500kb of susceptibility variants identified previously in women of European ancestry[2-14,16-19], leaving 314 variants from 27 regions associated with breast cancer at *P*<5x$10^{-8}$ (Supplementary Figures 1 and 2). The strongest associations were observed in a 610kb (b37 28,314,612- 28,928,858) interval on chromosome 22 (smallest *P*=8.2x$10^{-22}$, for rs62237573). This interval lies approximately 100kb centromeric to *CHEK2*, and further analysis revealed that the associated SNPs were correlated with the *CHEK2* founder variant 1100delC (strongest correlation $r^2$=0.39 for SNP rs62235635), *CHEK2* 1100delC is known to be associated with breast cancer through candidate gene analysis, but has not previously generated an association in GWAS [26,27]. We performed an analysis adjusting for *CHEK2* 1100delC using data on ~40,000 samples that had been genotyped for this variant. The strongest associated variant in this subset was rs140914118; after adjustment for 1100delC the statistical significance diminished markedly (*P*=3.1x$10^{-9}$ to *P*=0.78;Supplementary Figures 3a and 3b), suggesting that this signal is driven by *CHEK2* 1100delC.

Variants in four regions (*DNAJC1*, 5p12, *PTHLH* and *MKL1*) lay within 2Mb of a previously published susceptibility-associated SNP. In each case, these associations became weaker (no longer *P*<5x$10^{-8}$) after adjustment for the previously associated SNP(s) in the region (data not shown). For four other regions, the significant variants were identified in just one GWAS, and failed imputation ($r^2$<0.3) in the remaining datasets, including iCOGS; we did not consider these variants further.

To confirm the results for the remaining 18 regions, we performed re-imputation in the iCOGS dataset without phasing (See Online Methods). Fifteen loci remained associated with breast cancer at P<5x$10^{-8}$ (Table 1 and Supplementary Table 4). For three of the loci, the most significant SNP, or a highly correlated SNP, had been directly genotyped on iCOGS (Supplementary Table 5); one, rs11205277, had been included on the array because it is associated with adult height[28], while the other two were selected based on evidence from the combined breast cancer GWAS but failed to reach genome-wide significance in the earlier analyses. We attempted to genotype the 12 remaining variants on a subset of ~4K samples to confirm the quality of the imputation (10 variants could be directly genotyped, for one region an alternative correlated variant was selected (Supplementary Table 5). For the 11 variants that could be assessed, the $r^2$ between the observed and imputed genotypes were close to the $r^2$ estimated in the imputation. Furthermore, the estimated effect sizes in the subset of individuals that we genotyped were similar to those obtained from the imputed

genotypes (Supplementary Table 5). These results indicate that the analyses based on imputed genotype data were reliable.

There was little or no evidence of heterogeneity in the per-allele odds ratios (ORs) among studies genotyped using iCOGS (Supplementary Table 6 and Supplementary Figure 4). There was little evidence for departure from a log-additive model for any locus, except for a borderline departure for rs6796502 ($P$=0.049) for which the ORs for heterozygotes and homozygotes for the risk associated allele were similar (Supplementary Table 6).

The estimated ORs for invasive versus in-situ disease were similar for all the loci ($P$>0.05) (Supplementary Table 7). For four of the loci, rs12405132, rs12048493, rs4593472 and rs6507583 the association was stronger for ER positive disease (case only $P$<0.05) (Supplementary Table 8). Seven of the loci were associated with ER-negative disease ($P$<0.05) but none had a stronger association for ER-negative than ER-positive disease. Two of the loci showed significant trends in the OR by age at diagnosis: for rs13162653, the OR was higher at younger ages ($P$=0.007), while for rs6507583, the OR was higher at older ages ($P$=0.006) (Supplementary Table 9). One of the variants, chr17:29230520:D in *ATAD5* is correlated with a variant that has also been shown to be associated with serous ovarian cancer in a meta-analysis[29] ($r^2$=0.93 between chr17:29230520:D and chr17:29181220:I).

To approach the task of identifying the likely causal variants and genes underlying these associations, we first defined the set of all SNPs correlated with each of the 15 lead SNPs and that could not be ruled out as potentially causal (based on a likelihood ratio 100:1[30]), resulting in a subset of 522 variants (Supplementary Table 10). One of the variants, rs72755295, lies in an intron of *EXO1*, encoding a protein involved in mismatch repair. It is strongly correlated with only one other variant, rs4149909, coding for an amino-acid substitution in *EXO1* (p.Asn279Ser; CADD score 33[31]), suggesting that this variant is likely to be functionally related to breast cancer risk. None of the remaining SNPs lay within gene coding sequences, consistent with previous observations that most common cancer susceptibility variants are regulatory. For each of the remaining 520 variants, we then looked for enhancer elements in mammary cell lines, based on ENCODE ChIP-Seq data[32,33]. To identify potential gene targets, we combined this information with ENCODE ChIA-PET chromatin interaction data. We identified two regions in which the associated variants overlapped with putative enhancer sequences and for which consistent promoter interactions were predicted (Table 1). For rs12405132 at 1q21.1 , we identified four potential interacting genes, *RNF115*, *POLR3C*, *PDZK1* and *PIAS3* (Figure 2). Of these, the strongest evidence was for *RNF115* and *PDZK1;* three of the 64 potentially causal variants lay in interacting enhancer regions. *RNF115* (also known as *BCA2*) is an E3

ubiquitin ligase RING finger protein that is overexpressed in ER-positive breast cancers[34]. *PDZK1* is a scaffold protein that connects plasma membrane proteins and regulatory components, regulating their surface expression in epithelial cells apical domains, and has been proposed to act as an oncogene in breast cancer[35].

SNPs correlated with rs6507583 at 18q12.3 lay in regions interacting with the promoter of *SETBP1* (Supplementary Figure 5). The encoded protein has been shown to bind the SET nuclear oncogene which is involved in DNA replication.

We utilised data from TCGA to assess associations between the 15 novel susceptibility variants and expression of neighbouring genes in breast tumors and normal breast tissue. One SNP, rs7707921, was strongly associated with *RPS23* expression in all tissues (Supplementary Table 11, Supplementary Figure 6). However, stronger associations with expression were observed with more telomeric SNPs that were less strongly associated with disease risk (top eQTL SNP rs3739: $P=10^{-23}$, $P$-risk=$5.28\times10^{-7}$), suggesting that this association may be coincidental. SNP, rs7707921 was also more weakly associated with expression of *ATP6AP1L* ($P=5.6\times10^{-5}$ in tumours, $P=0.066$ in normal tissue).

Based on the estimated ORs in the iCOGS stage (all but one of which were in the range 1.05-1.10), the 15 novel loci identified here would explain a further ~2% of the 2-fold familial risk of breast cancer. Taken together with previously identified loci, more than 90 independent common susceptibility loci for breast cancer have been identified, explaining ~16% of the familial risk. We estimate assuming a log-additive model that, based on genotypes for variants at these loci, approximately 5% of women in the general population have a >2 fold increased risk of breast cancer and 0.7% of women have a >3 fold increased risk. In the current analyses, more than 50% of variants with MAF>0.005 in subjects of European ancestry were well imputable ($r^2>0.5$) These results suggest that, while there may be further susceptibility variants with comparable associated effects that were not well imputed, the identification of many additional loci will require larger association studies. In the meantime, inclusion of these additional loci in polygenic risk scores will improve our ability to discriminate between high and low risk individuals, potentially improving breast cancer screening and prevention.

**URLs**

BCAC http://ccge.medschl.cam.ac.uk/consortia/bcac/index.html

COGS http:// http://www.cogseu.org/

ENCODE http://www.genome.gov/encode/, genome.ucsc.edu/ENCODE/

iCOGS http://www.nature.com/icogs/, http://ccge.medschl.cam.ac.uk/research/consortia/icogs/

IMPUTE http://mathgen.stats.ox.ac.uk/impute/impute.html

MACH http://www.sph.umich.edu/csg/abecasis/MACH/

SHAPEIT https://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html

TCGA http://cancergenome.nih.gov/

1000 genomes: http://www.1000genomes.org/

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**Author Contributions**

K.Michailidou and D.F.E. performed the statistical analysis and drafted the manuscript. D.F.E. conceived and coordinated the synthesis of the iCOGS array and led the BCAC. P.H. coordinated the Collaborative Oncological Gene-Environment Study (COGS). J.Benitez led the iCOGS genotyping working group. A.G.-N., G.P., M.R.A., J.Benitez, D.V., F.B., D.C.T., J.Simard, A.M.D., C.L., C.Baynes, S.A, C.S.H and M.J.M. co-ordinated genotyping of the iCOGS array. M.G-C., P.D.P.P. and M.K.S. led the BCAC pathology and survival working group . J.C-C. led the BCAC risk factor working group. A.M.D. and G.C.-T. led the iCOGS quality control working group. J. Beesley, J.D and M.J.L. provided

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**Competing Financial Interests**

The authors confirm that they have no competing financial interests

**Figure Legends**

**Figure 1**: Histograms of the imputation $r^2$ **a)** Histogram of the imputation $r^2$ for the iCOGS for variants with MAF>0.05 **b)** Histogram of the imputation $r^2$ for the UK2 GWAS for variants with MAF>0.05 **c)** Histogram of the imputation $r^2$ for the iCOGS for variants with MAF<=0.05 **d)** Histogram of the imputation $r^2$ for the UK2 GWAS for variants with MAF<=0.05.

**Figure 2**: The chromosome 1 locus tagged by rs12405132 **a)** The Manhattan Plot displays the strength of genetic association ($-\log_{10} P$ ) versus chromosomal position (Mb), where each dot presents a genotyped (solid black dot) or imputed (red circle) SNP (in the iCOGS stage). The purple horizontal line represents the threshold for genome-wide significance ($P=5\times10^{-8}$). Gene structures are depicted as well as the location of SNPs with MAF>0.01 which were neither imputed reliably nor genotyped. **b)** Mammary cell enhancer locations as defined in Corradin et al.[32], and Hnisz et al.[33], are shown where elements overlapping the best associated SNPs are labelled with their predicted target genes. A subset of ChiA-PET interactions in MCF7 cells (mediated by either RNApolII or ERa) between enhancers and their target gene promoters are also shown.

| Best variant | Locus | Position[2] | Alleles[3] | EAF[4] | r[2(5)] | GWAS OR (95% CI)[6] | GWAS P[7] | iCOGS OR (95% CI) | iCOGS P | Combined GWAS + iCOGS P | Genes within +/-2kb | Enhancers in MCF7/HMEC | eQTLs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs12405132 | 1q21.1 | 145644984 | C/T | 0.36 | 0.96 | 0.96 (0.92-0.99) | 0.00962 | 0.95 (0.93-0.97) | $2.34x10^{-7}$ | $7.92x10^{-9}$ | *LOC10028814, NBPF10, RNF115* | *RNF115*, *POLR3C*,*PDZK1, PIAS3* | - |
| rs12048493 | 1q21.2 | 149927034 | A/C | 0.34 | 0.76 | 1.04 (0.99-1.09) | 0.121 | 1.07 (1.05-1.10) | $1.66x10^{-9}$ | $1.10x10^{-9}$ | - | - | - |
| rs72755295 | 1q43 | 242034263 | A/G | 0.03 | 0.94 | 1.19 (1.03-1.39) | 0.021 | 1.15 (1.09-1.22) | $2.60x10^{-7}$ | $1.82x10^{-8}$ | *EXO1* | - | - |
| rs6796502 | 3p21.3 | 46866866 | G/A | 0.09 | 0.91 | 0.92 (0.87-0.98) | 0.00657 | 0.92 (0.89-0.95) | $8.13x10^{-7}$ | $1.84x10^{-8}$ | - | - | - |
| rs13162653 | 5p15.1 | 16187528 | G/T | 0.45 | 0.72 | 0.92 (0.88-0.95) | $5.18x10^{-6}$ | 0.95 (0.93-0.97) | $1.71x10^{-6}$ | $1.08x10^{-10}$ | - | - | - |
| rs2012709 | 5p13.3 | 32567732 | C/T | 0.46 | 0.81 | 1.06 (1.02-1.09) | 0.00101 | 1.05 (1.03-1.08) | $1.66x10^{-6}$ | $6.38x10^{-9}$ | - | - | - |
| rs7707921 | 5q14 | 81538046 | A/T | 0.23 | 0.88 | 0.94 (0.9-0.98) | 0.00302 | 0.93 (0.91-0.95) | $4.09x10^{-9}$ | $5.00x10^{-11}$ | *ATG10* | - | *RPS23, ATP6AP1L* |
| rs9257408 | 6p22.1 | 28926220 | G/C | 0.38 | 0.92 | 1.05 (1-1.1) | 0.0372 | 1.05 (1.03-1.08) | $4.53x10^{-7}$ | $4.84x10^{-8}$ | - | - | - |
| rs4593472 | 7q32.3 | 130667121 | C/T | 0.35 | 1.00 | 0.92 (0.88-0.96) | $2.57x10^{-5}$ | 0.95 (0.94-0.97) | $3.97x10^{-6}$ | $1.83x10^{-9}$ | *FLJ43663* | - | - |
| rs13365225 | 8p11.23 | 36858483 | A/G | 0.17 | 0.94 | 0.89 (0.85-0.93) | $6.32x10^{-7}$ | 0.95 (0.93-0.98) | 0.000159 | $1.06x10^{-8}$ | - | - | - |
| rs13267382 | 8q23.3 | 117209548 | G/A | 0.36 | 0.97 | 1.07 (1.03-1.12) | 0.000537 | 1.05 (1.03-1.07) | $4.87x10^{-6}$ | $1.72x10^{-8}$ | *LINC00536* | - | - |
| rs11627032 | 14q32.12 | 93104072 | T/C | 0.26 | 0.73 | 0.94 (0.9-0.98) | 0.00114 | 0.94 (0.92-0.96) | $1.06x10^{-6}$ | $4.48x10^{-9}$ | *RIN3* | - | - |
| chr17:29230520 :D | 17q11.2 | 29230520 | GGT/G | 0.20 | 0.77 | 0.94 (0.89-0.98) | 0.009 | 0.93 (0.91-0.96) | $1.11x10^{-6}$ | $3.34x10^{-8}$ | *ATAD5* | - | - |
| rs745570 | 17q25.3 | 77781725 | A/G | 0.50 | 0.93 | 0.94 (0.91-0.98) | 0.000754 | 0.95 (0.93-0.97) | $4.52x10^{-7}$ | $1.40x10^{-9}$ | - | - | - |
| rs6507583 | 18q12.3 | 42399590 | A/G | 0.07 | 0.96 | 0.91 (0.85-0.98) | 0.00803 | 0.91 (0.88-0.95) | $1.21x10^{-6}$ | $3.20x10^{-8}$ | *SETBP1* | *SETBP1* | - |

**Table 2**: Results for the 15 regions with combined $P<5x10^{-8}$. Results are shown for the strongest associated variant in the region.

[1] Chromosome

[2] Build 37 position

[3] Reference/effect allele, based on the forward strand

[4] Mean effect allele frequency over all controls

[5] Imputation $r^2$ in the iCOGS samples (calculated by the average info score from IMPUTEv2)

[6] Per allele odds ratio for the minor allele relative to the major allele

[7] P value for the 1df trend test

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**Online Methods**

Details of the subjects, genotyping and QC measures for the GWAS and iCOGS data are described elsewhere[12,14,16,36,37]. All participating studies were approved by their appropriate ethics review board and all subjects provided informed consent. Analyses were restricted to women of European ancestry. All imputations were performed using the 1000 Genomes Project March 2012 release as the reference panel. Of the 11 GWAS, 8 (C-BCAC) plus a subset of the BPC3 GWAS (CGEMS) were used in the combined GWAS analysis that nominated 29,807 SNPs for the array. The BPC3 and TNBCC GWAS nominated additional SNPs with evidence for association with ER-negative or triple-negative (ER-, PR- and HER2- negative) breast cancer. The EBCG GWAS was not used to nominate SNPs for the iCOGS array.

For eight GWAS (C-BCAC), genotypes were imputed in a two-stage procedure, using SHAPEIT to derive phased genotypes and IMPUTEv2 to perform the imputation on the phased data [22]. We performed the imputation using 5Mb non-overlapping intervals for the whole genome. OR estimates and standard errors where obtained using logistic regression with SNPTEST [21]. For two of the studies we adjusted for the 3 leading principal components as it was found to reduce materially the inflation factor; for the rest of the studies no such adjustment was necessary. For the remaining three GWAS (BPC3, TNBCC and EBCG), imputation was performed using MACH and Minimac[23].Genomic control adjustment was applied to each GWAS as previously described[16]. The iCOGS data were also imputed in a two-stage procedure using SHAPEIT and IMPUTEv2, again using 5Mb non-overlapping intervals. We split the ~90K samples into 10 subsets, where possible keeping subjects from the same study in the same subset. We obtained OR estimates and standard errors using logistic regression adjusting for study and 9 principal components.

For the regions showing evidence of association we repeated the imputation in iCOGS, using IMPUTEv2 but without pre-phasing in SHAPEIT to improve imputation accuracy. We also increased the number of MCMC iterations from 30 to 90, and increased the buffer region from 250kb to 500kb.

*Meta-analysis*

OR estimates and standard errors were combined in a fixed effects inverse variance meta-analysis using METAL[23]. For the GWAS, results were included in the analysis for all SNPs with MAF>0.01 and imputation $r^2$>0.3, except for the TN GWAS where the criteria were $r^2$>0.9 and MAF>0.05. For iCOGS, we included all SNPs with $r^2$>=0.3 and MAF>0.005.

*Confirmatory genotyping*

The best variant in each region after the re-imputation and meta-analysis was genotyped in 4123 samples from SEARCH, using Taqman according to the manufacturer's instructions. The squared correlations between the observed genotypes and the genotypes estimated by imputation are shown in Supplementary Table 5. For all the imputed SNPs the squared correlations was greater than 0.7, the call-rates were >=0.98 and there was no evidence of departure of genotype frequencies from those expected under HWE (p>0.1).

*eQTL analyses*

Germline genotype, mRNA expression, and somatic copy number data for samples taken from breast tumours and tumour-adjacent normal tissue were obtained from The Cancer Genome Atlas[38]. The copy number and genotype data were measured using the Affymetrix Genome-Wide Human SNP 6.0 platform. For the mRNA expression data, we used the expression profiles obtained using the Agilent G4502A-07-3 microarray. The genotype data were subjected to the following quality control filters. SNPs were excluded in case of low frequency (MAF < 1%), low call rate (< 95%,) or departure from Hardy-Weinberg equilibrium at $P < 1 \times 10^{-13}$. Individuals were excluded based on low call rate (< 95%), or high heterozygosity (false discovery rate < 1%). Furthermore, individuals were also excluded in case of non-European ancestry, or male gender. Quality control and intersection with the other genomic data types resulted in 380 tumour samples and 56 normal samples.

The genotype data were imputed as described above. eQTL analysis was performed using linear regression with SNPTEST, regressing the mRNA expression of selected candidate genes on the imputed genotype. For each gene, we performed the eQTL analysis against every microarray probe that uniquely maps to that gene. We adjusted the analyses for somatic copy number of the gene, and for SNPs that intersect the probe sequence, provided that their MAF exceeds 1% in individuals of European ancestry in the 1,000 Genomes data.

*Enhancer analyses*

Maps of enhancer regions with predicted target genes were obtained from Hnisz et al.[33], and Corradin et al.[32]. Enhancers active in the mammary cell types MCF7, HMEC and HCC1954 were intersected with candidate causal variants using Galaxy. ENCODE ChIA-PET chromatin interaction data from MCF7 cells (mediated by RNApolII and ER$\alpha$) were downloaded using the UCSC Table browser. Galaxy was used to identify ChIA-PET interactions between an implicated mammary cell enhancer (containing a strongly associated variant) and a predicted gene promoter (defined as regions 3 kb upstream and 1 kb downstream of the transcription start site).

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# Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer

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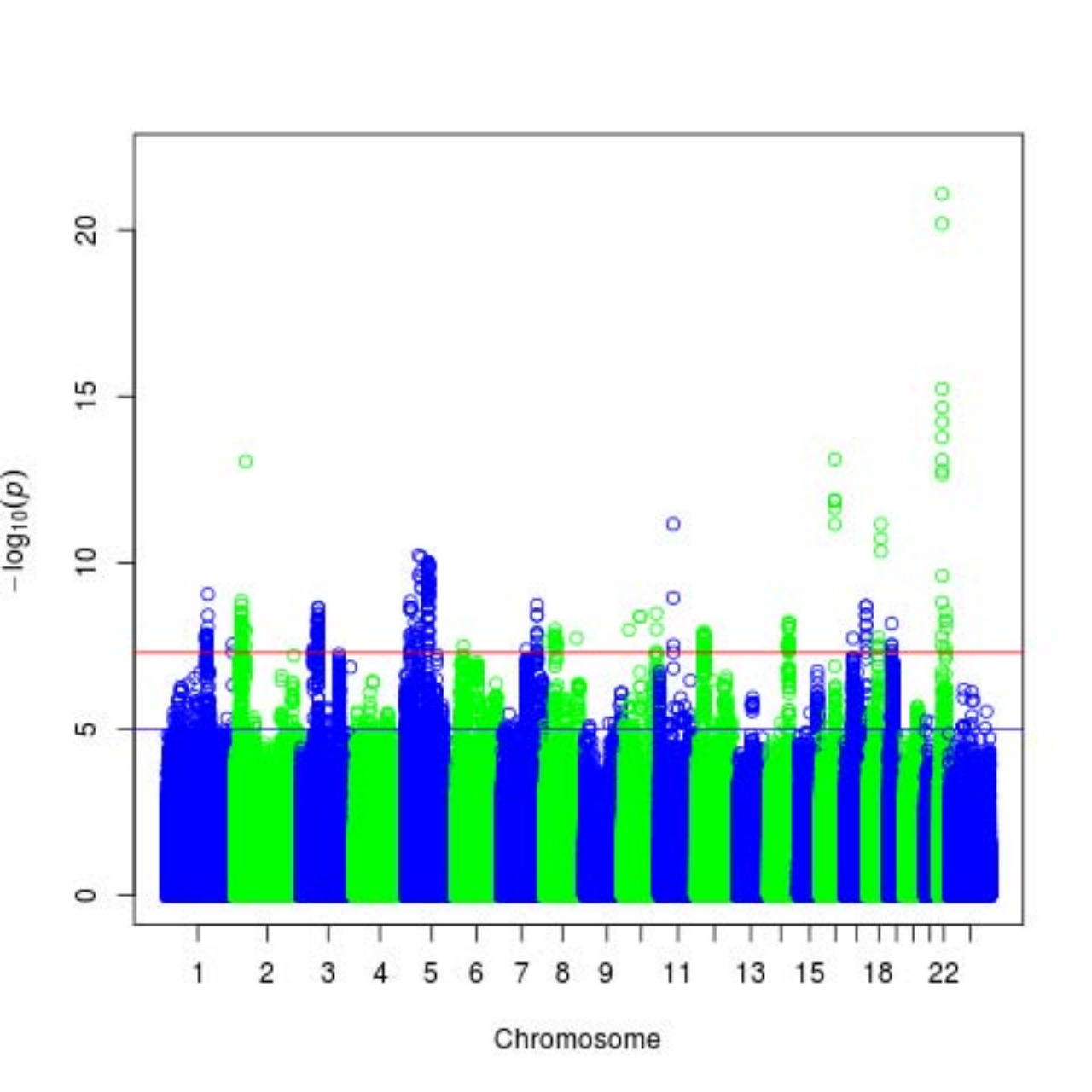
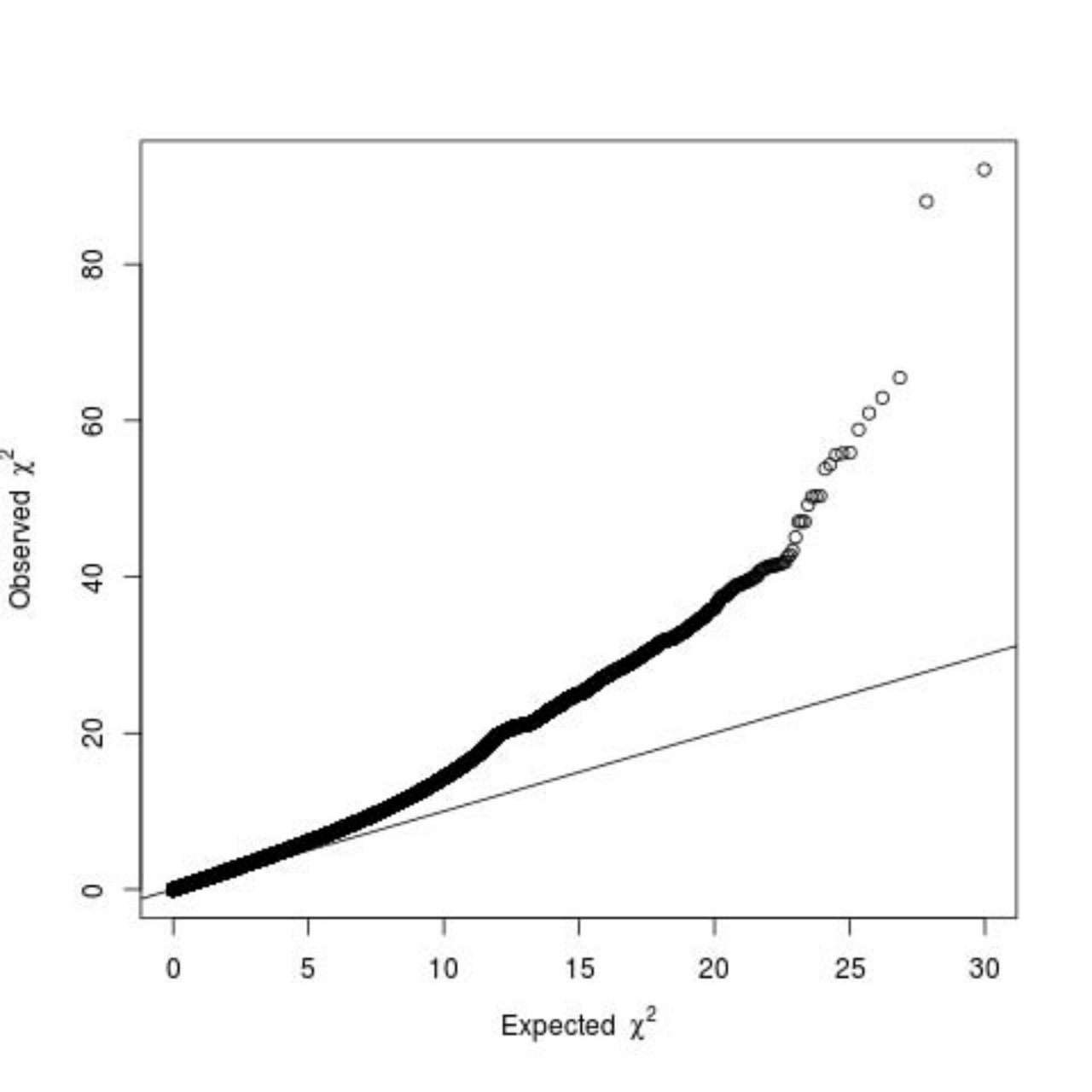
## Supplementary Material

**Supplementary Figure 1**: Manhattan Plots for the strength of genetic association ($-\log_{10}P$) versus chromosomal position, where each dot represents a single variant. The association tests are from the meta-analysis of the GWAS and iCOGS datasets (see Online Methods). Variants within 500kb of variants previously established to be associated with breast cancer were removed (see text). Red horizontal line corresponds to the $P=5\times10^{-8}$, blue horizontal line corresponds to $P=10^{-5}$.

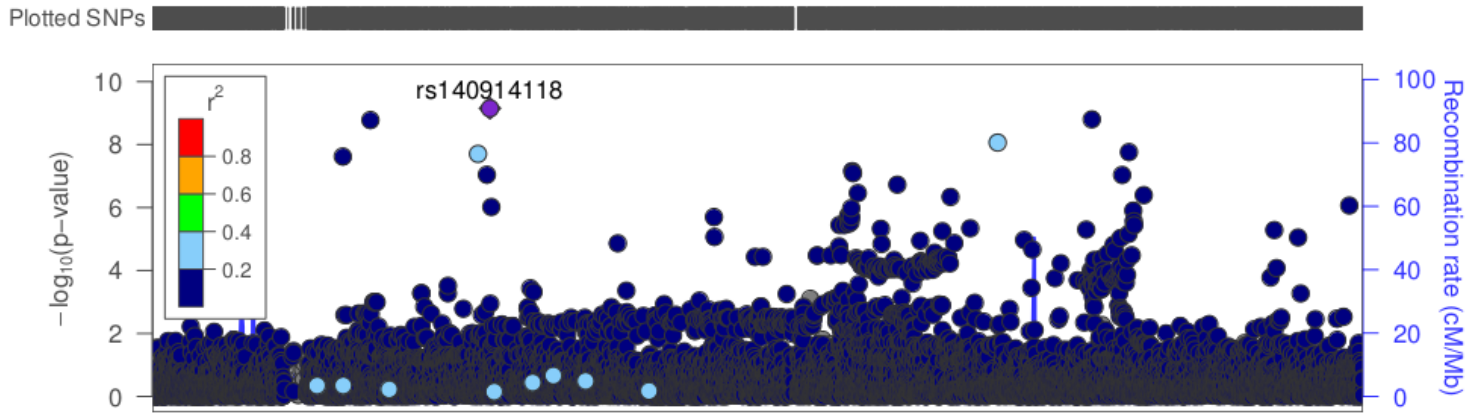

$-\log_{10}(p)$
0
5
10
15
20
1
2
3
4
5
6
7
8
9
11
13
15
18
22
Chromosome

**Supplementary Figure 2**: Quantile-quantile plot of the observed vs. expected chi-squared statistics for the meta-analysis of the combined GWAS and iCOGS results. Variants within 500kb of previously established breast cancer susceptibility loci were removed. Each circle represents the chi-squared statistic for a single variant. The blue diagonal line represents the predicted association statistics under the global null hypothesis of no association.

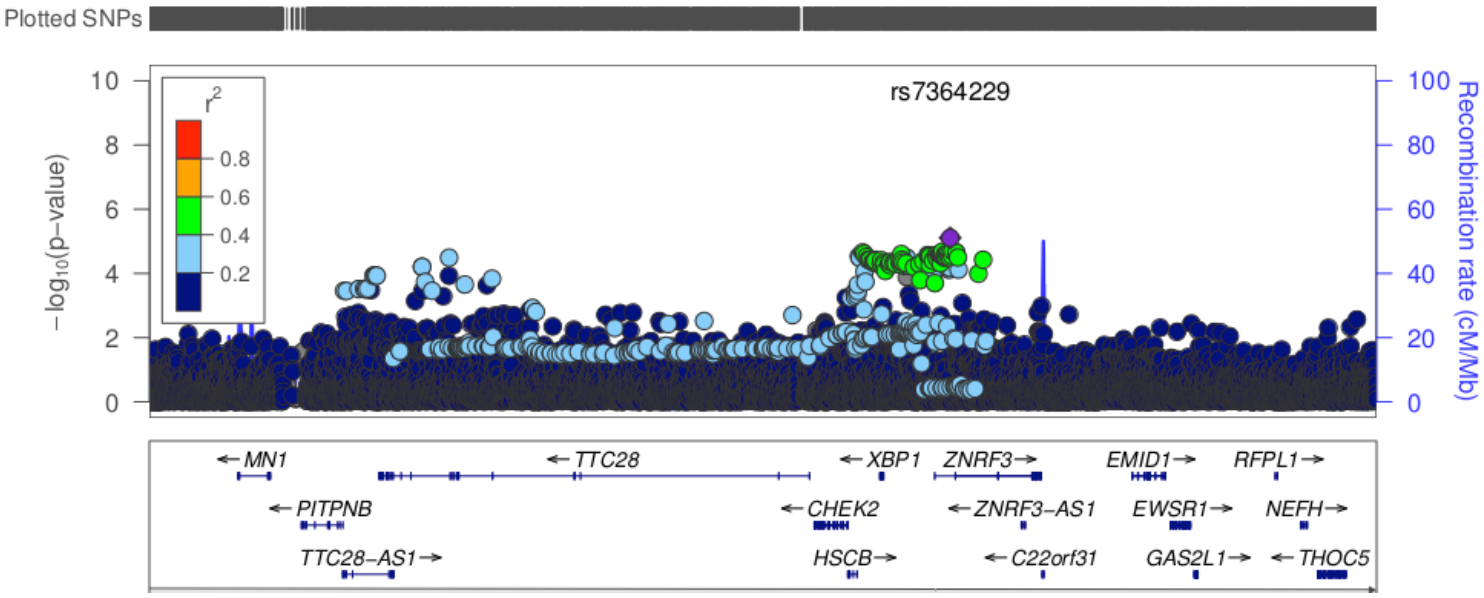

Observed $\chi^2$
0
20
40
60
80
0
5
10
15
20
25
30
Expected $\chi^2$

**Supplementary Figure 3: a)** Manhattan Plot of associations for the results in the *CHEK2* region (chromosome 22, b37: 280,000,000-30,121,477), in the subset of individuals that had both iCOGS and the *CHEK2**1100delC variant genotyped **b)** Manhattan Plot of associations for the (chromosome 22, b37: 280,000,000-30,121,477) region, after adjusting for *CHEK*2*1100delC.

**a)**

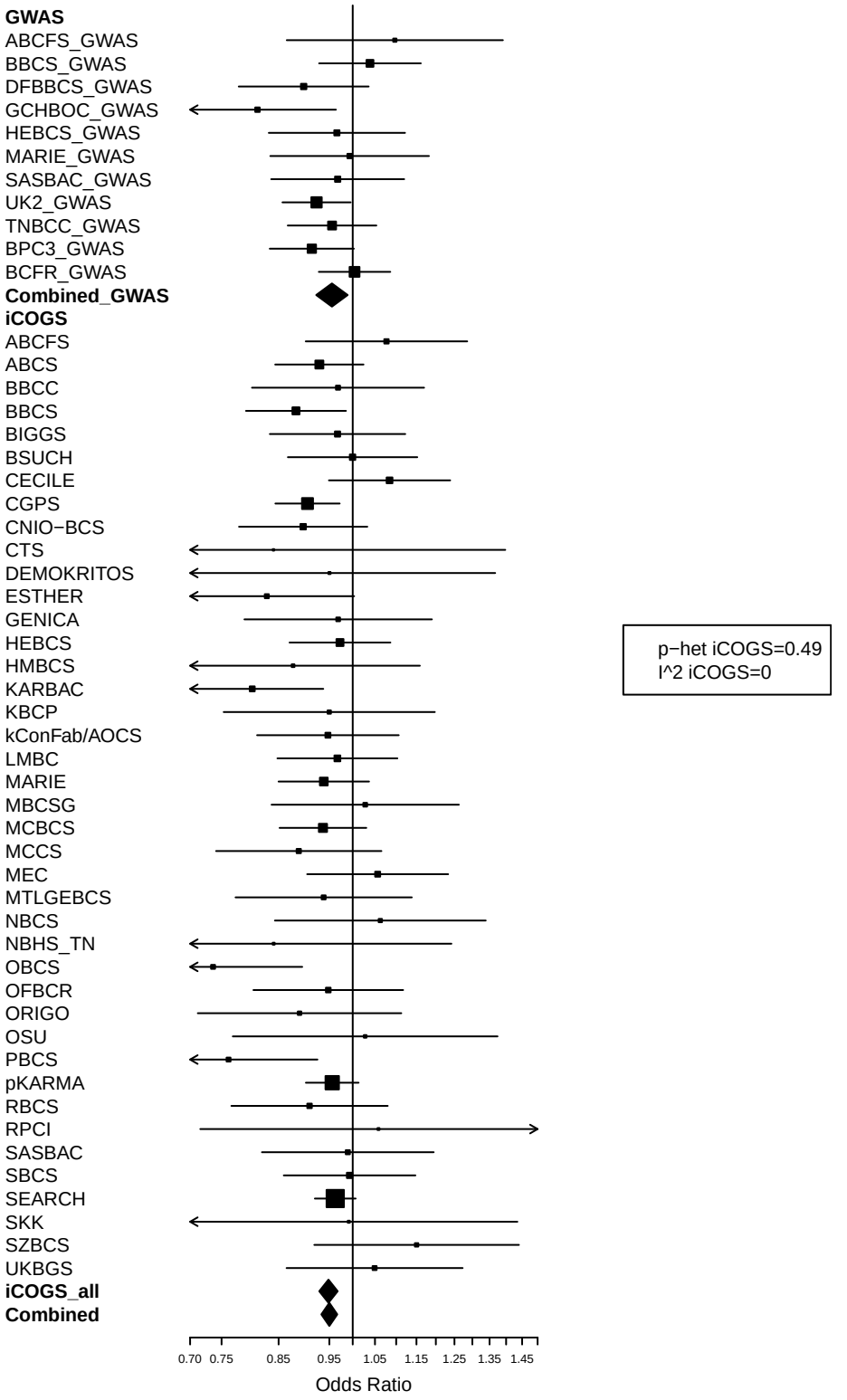

Plotted SNPs
rs140914118
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
0
20
40
60
80
100

**b)**


Plotted SNPs
rs7364229
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
0
20
40
60
80
100
MN1
TTC28
XBP1
ZNRF3
EMID1
RFPL1
PITPNB
CHEK2
ZNRF3−AS1
EWSR1
NEFH
TTC28−AS1
HSCB
C22orf31
GAS2L1
THOC5

**Supplementary Figure 4**: Forest plots for the 15 loci achieving genome-wide significance. Squares denote the estimated per-allele odds ratio for the minor allele in Europeans. The horizontal lines denote 95% confidence intervals. The area of the square is inversely proportional to the variance of the estimate. The diamond denotes the estimated per-allele OR from the combined analyses. $I^2$ and heterogeneity *P*-values were calculated in the iCOGS studies alone.

# rs12405132


GWAS
ABCFS_GWAS
BBCS_GWAS
DFBBCS_GWAS
GCHBOC_GWAS
HEBCS_GWAS
MARIE_GWAS
SASBAC_GWAS
UK2_GWAS
TNBCC_GWAS
BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
CNIO−BCS
CTS
DEMOKRITOS
ESTHER
GENICA
HEBCS
HMBCS
KARBAC
KBCP
kConFab/AOCS
LMBC
MARIE
MBCSG
MCBCS
MCCS
MEC
MTLGEBCS
NBCS
NBHS_TN
OBCS
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
p−het iCOGS=0.49
I^2 iCOGS=0
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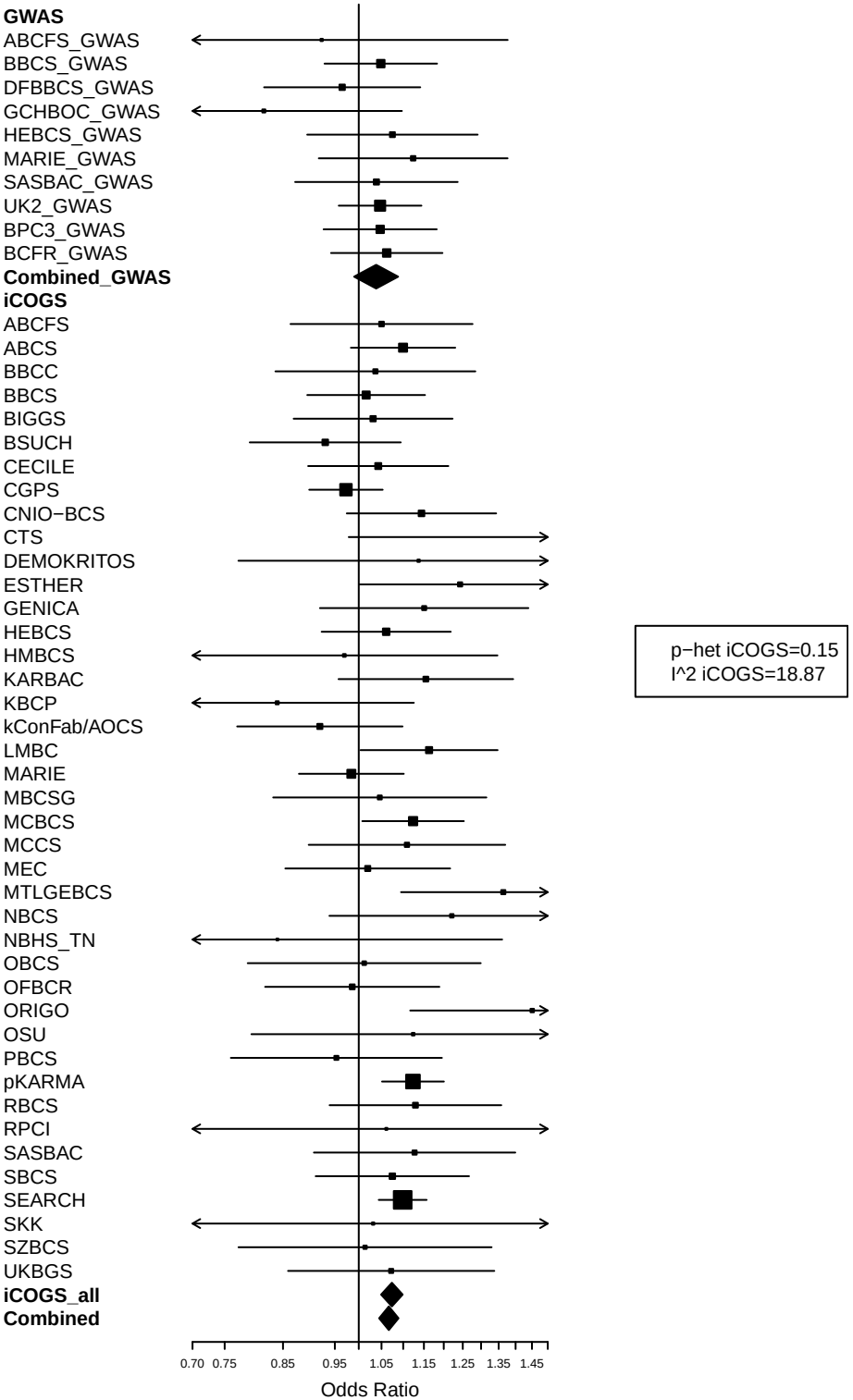
Odds Ratio

**rs12048493**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BBCS_GWAS
DFBBCS_GWAS
GCHBOC_GWAS
HEBCS_GWAS
MARIE_GWAS
SASBAC_GWAS
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BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
CNIO−BCS
CTS
DEMOKRITOS
ESTHER
GENICA
HEBCS
HMBCS
KARBAC
KBCP
kConFab/AOCS
LMBC
MARIE
MBCSG
MCBCS
MCCS
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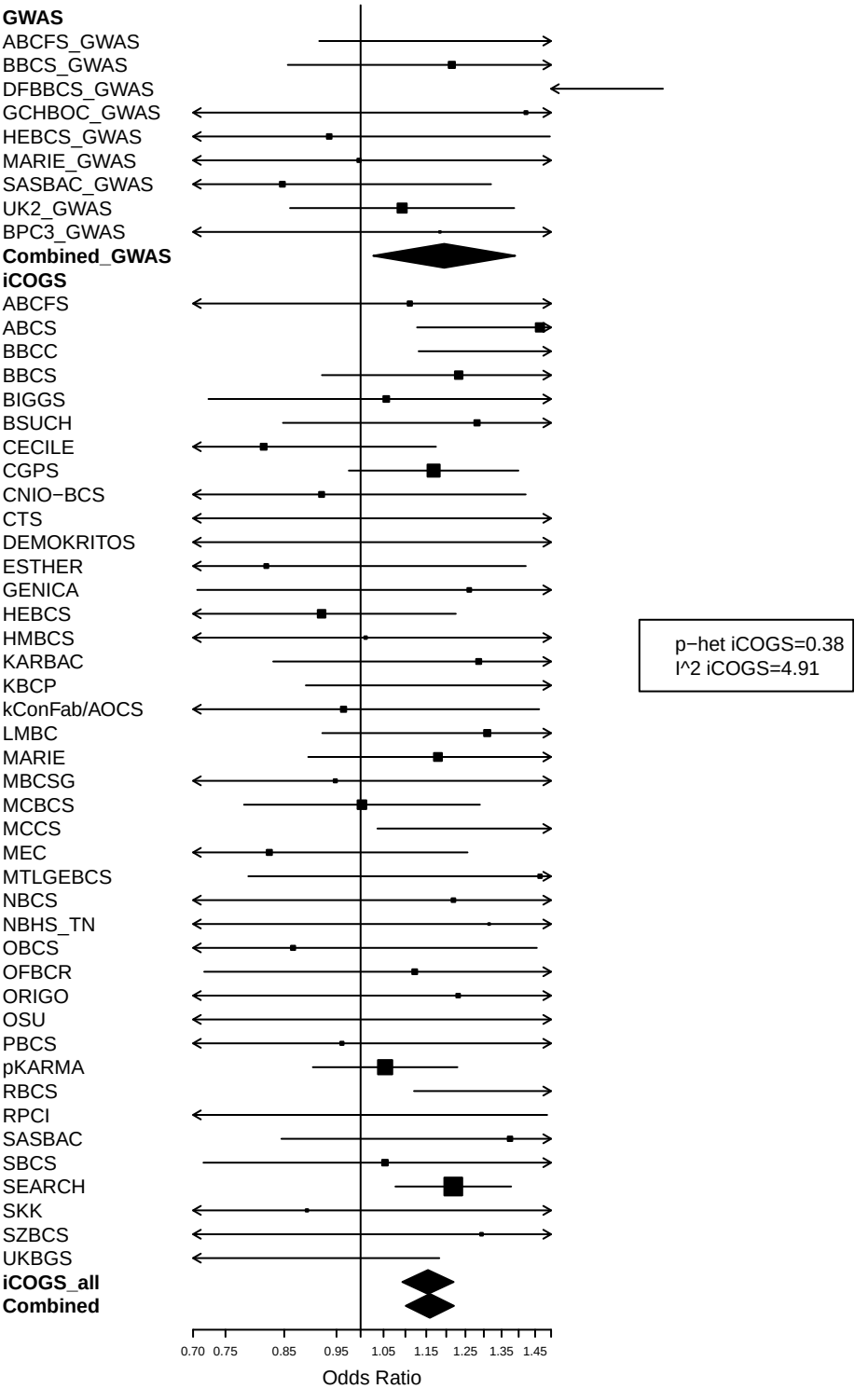
NBCS
NBHS_TN
OBCS
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
p−het iCOGS=0.15
I^2 iCOGS=18.87

**rs72755295**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BBCS_GWAS
DFBBCS_GWAS
GCHBOC_GWAS
HEBCS_GWAS
MARIE_GWAS
SASBAC_GWAS
UK2_GWAS
BPC3_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
CNIO−BCS
CTS
DEMOKRITOS
ESTHER
GENICA
HEBCS
HMBCS
KARBAC
KBCP
kConFab/AOCS
LMBC
MARIE
MBCSG
MCBCS
MCCS
MEC
MTLGEBCS
NBCS
NBHS_TN
OBCS
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
p−het iCOGS=0.38
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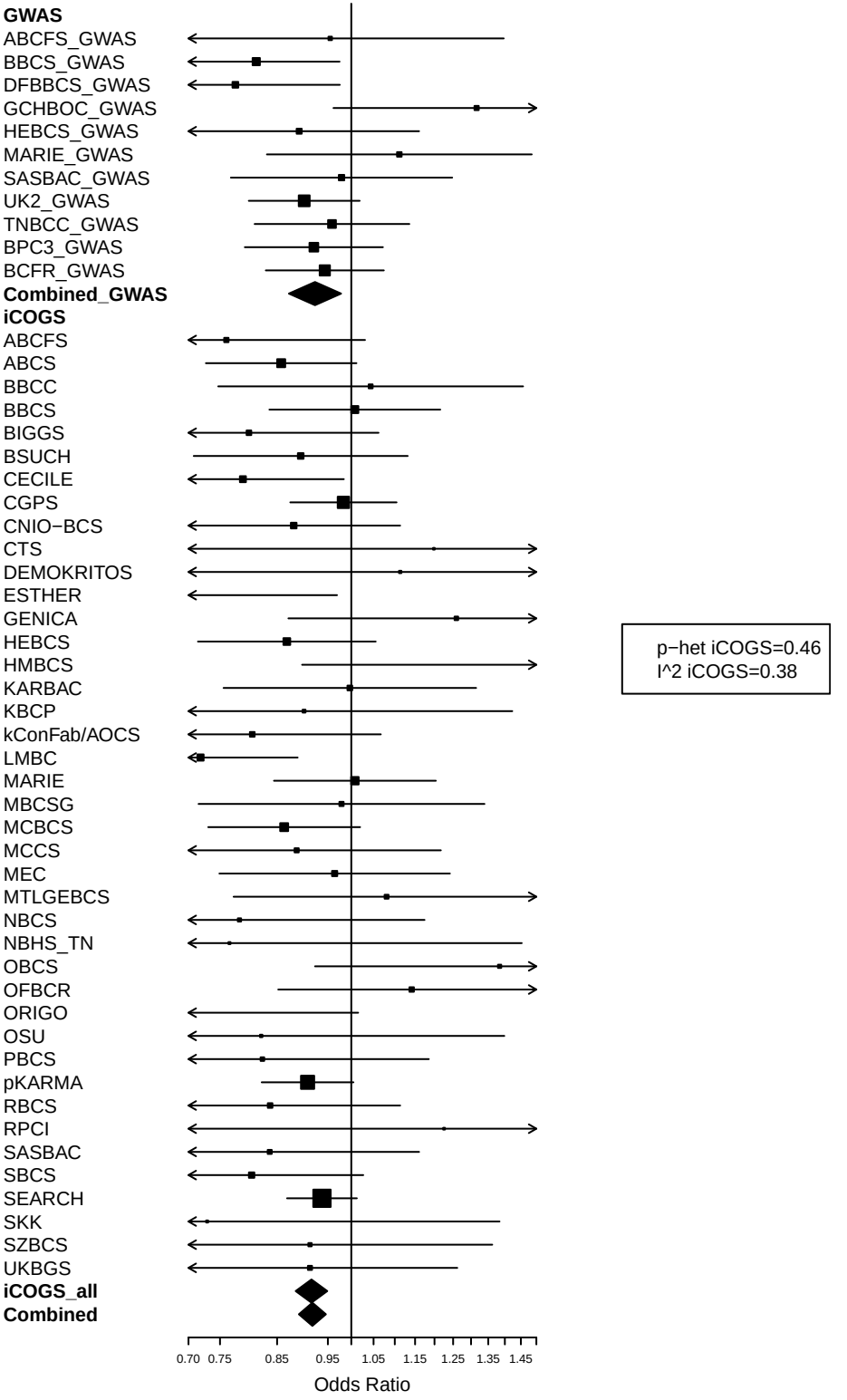
Odds Ratio

# rs6796502


GWAS
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BBCS_GWAS
DFBBCS_GWAS
GCHBOC_GWAS
HEBCS_GWAS
MARIE_GWAS
SASBAC_GWAS
UK2_GWAS
TNBCC_GWAS
BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
CNIO−BCS
CTS
DEMOKRITOS
ESTHER
GENICA
HEBCS
HMBCS
KARBAC
KBCP
kConFab/AOCS
LMBC
MARIE
MBCSG
MCBCS
MCCS
MEC
MTLGEBCS
NBCS
NBHS_TN
OBCS
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
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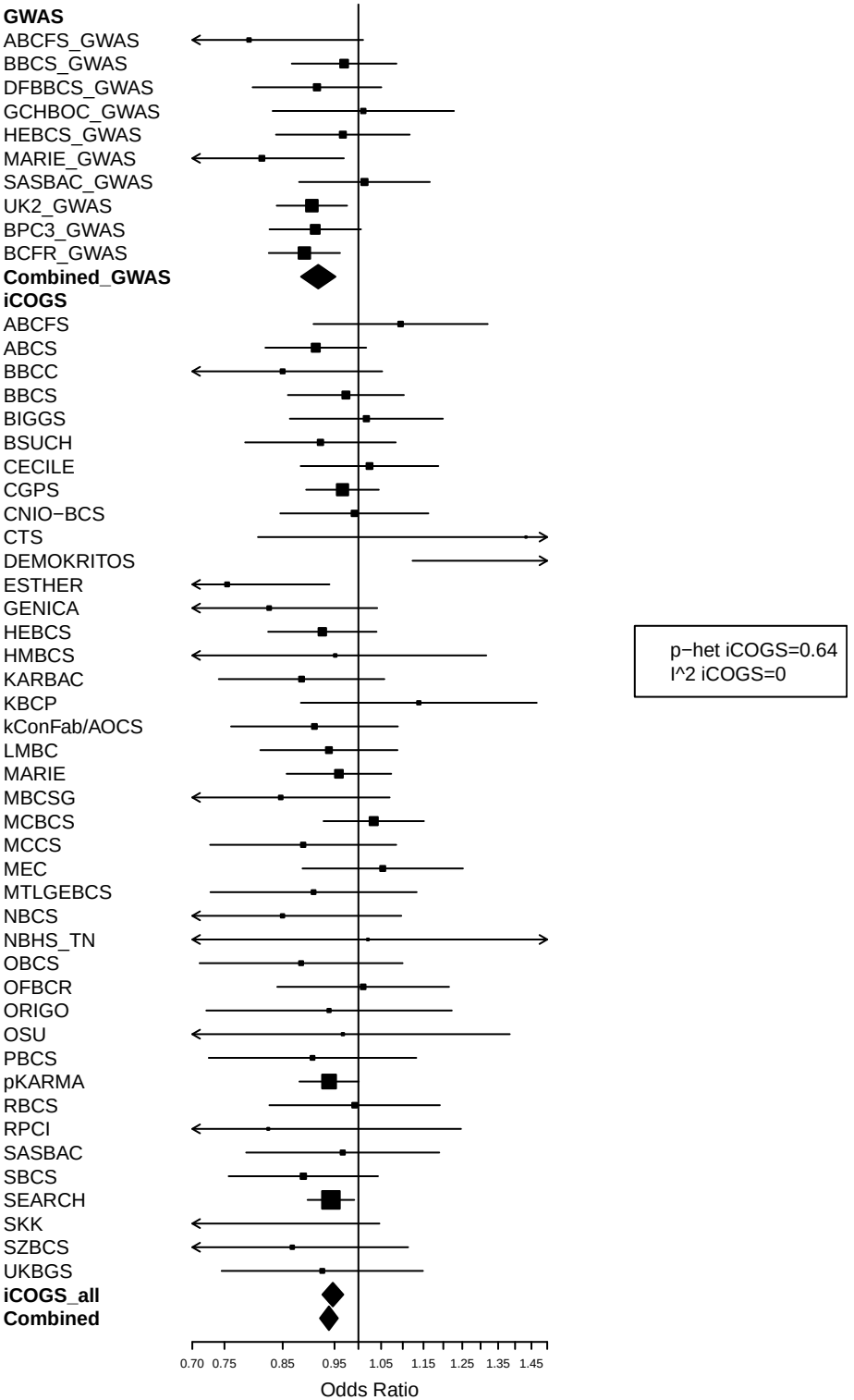
I^2 iCOGS=0.38

**rs13162653**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DFBBCS_GWAS
GCHBOC_GWAS
HEBCS_GWAS
MARIE_GWAS
SASBAC_GWAS
UK2_GWAS
BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
CNIO−BCS
CTS
DEMOKRITOS
ESTHER
GENICA
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KARBAC
KBCP
kConFab/AOCS
LMBC
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MCBCS
MCCS
MEC
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NBCS
NBHS_TN
OBCS
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
p−het iCOGS=0.64
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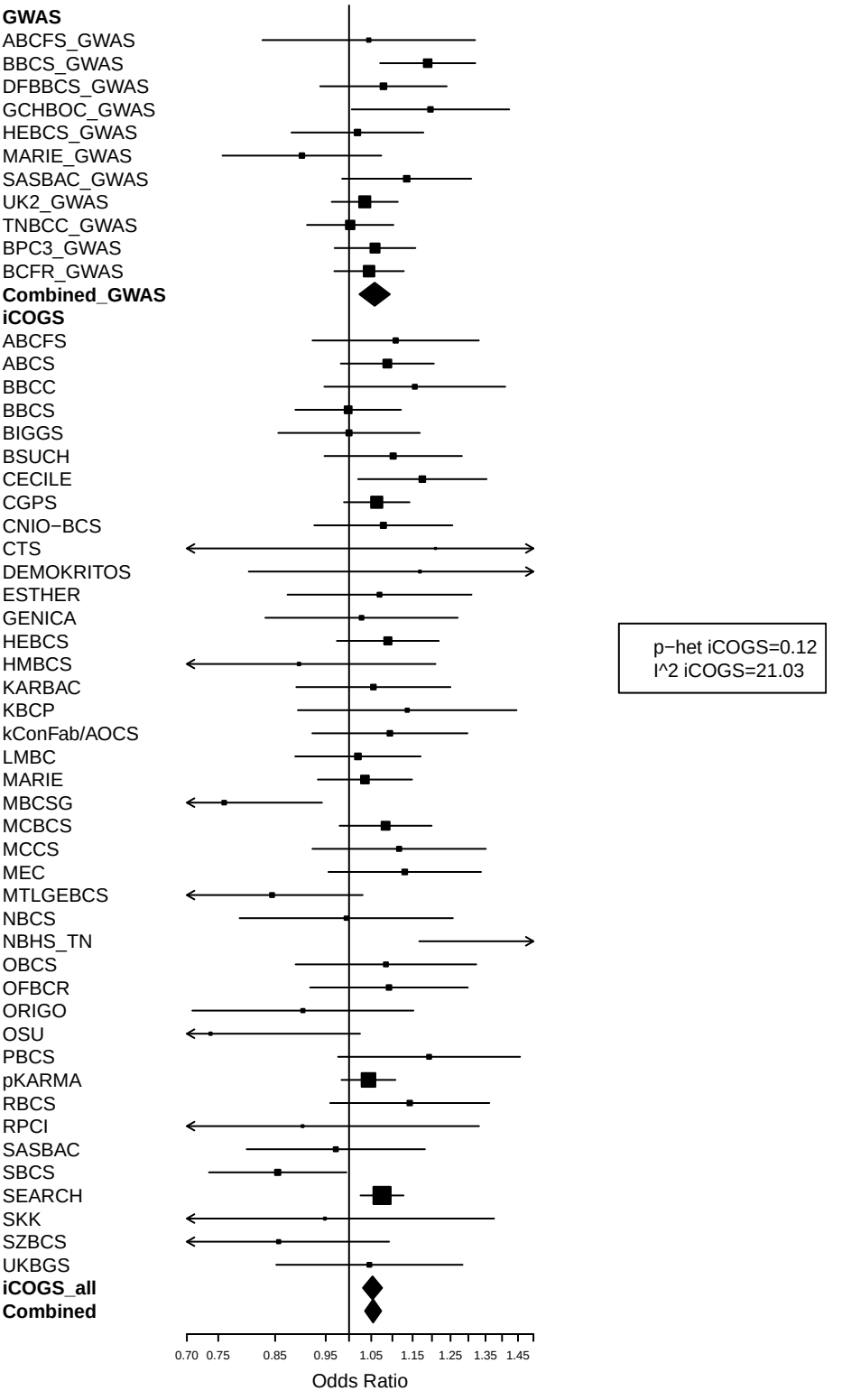
Odds Ratio

# rs2012709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DFBBCS_GWAS
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HEBCS_GWAS
MARIE_GWAS
SASBAC_GWAS
UK2_GWAS
TNBCC_GWAS
BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
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CECILE
CGPS
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ESTHER
GENICA
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kConFab/AOCS
LMBC
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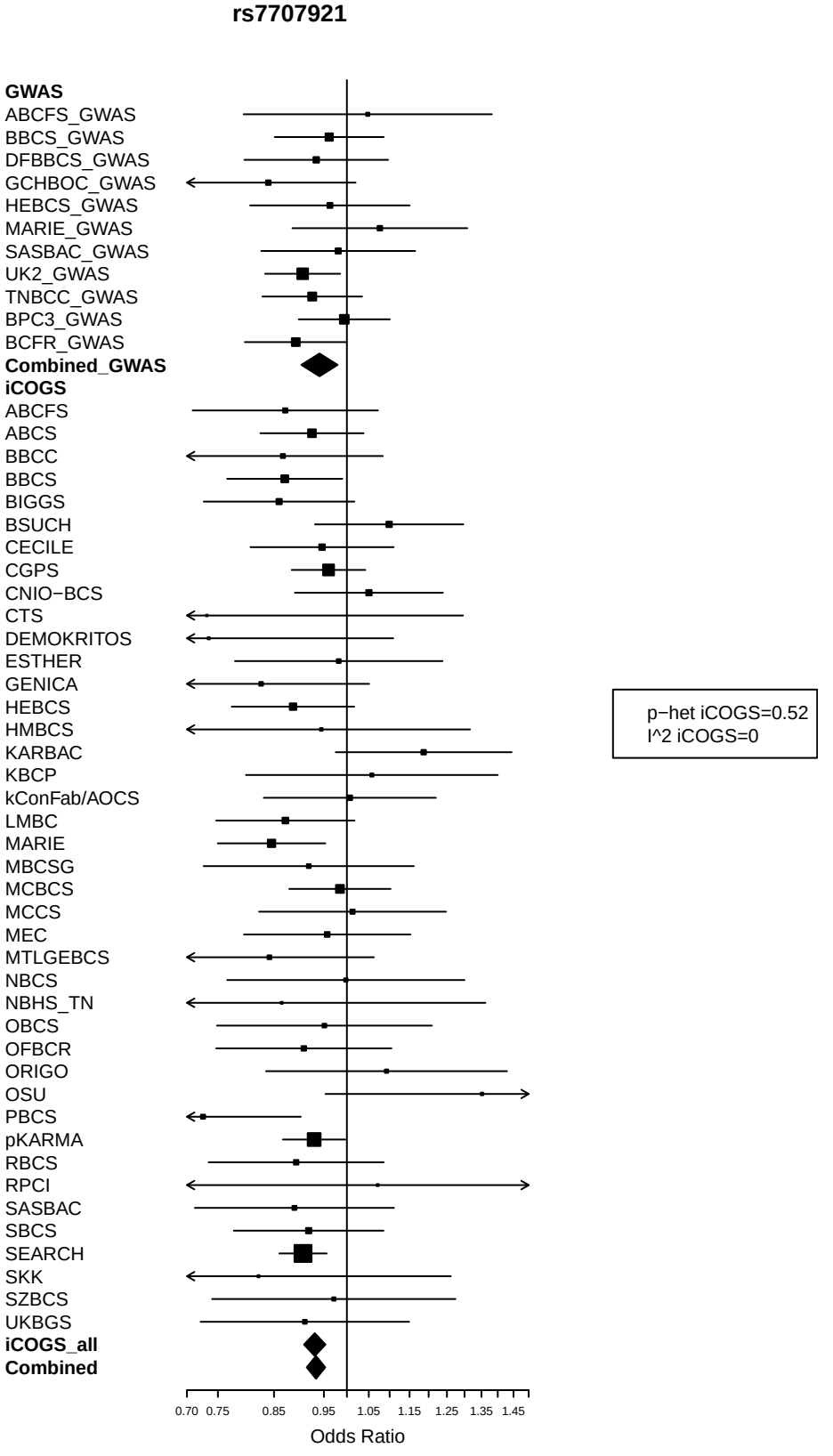
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
p−het iCOGS=0.12
I^2 iCOGS=21.03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MARIE_GWAS
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UK2_GWAS
TNBCC_GWAS
BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
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CTS
DEMOKRITOS
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GENICA
HEBCS
HMBCS
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KBCP
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LMBC
MARIE
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MCCS
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ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
p−het iCOGS=0.52
I^2 iCOGS=0
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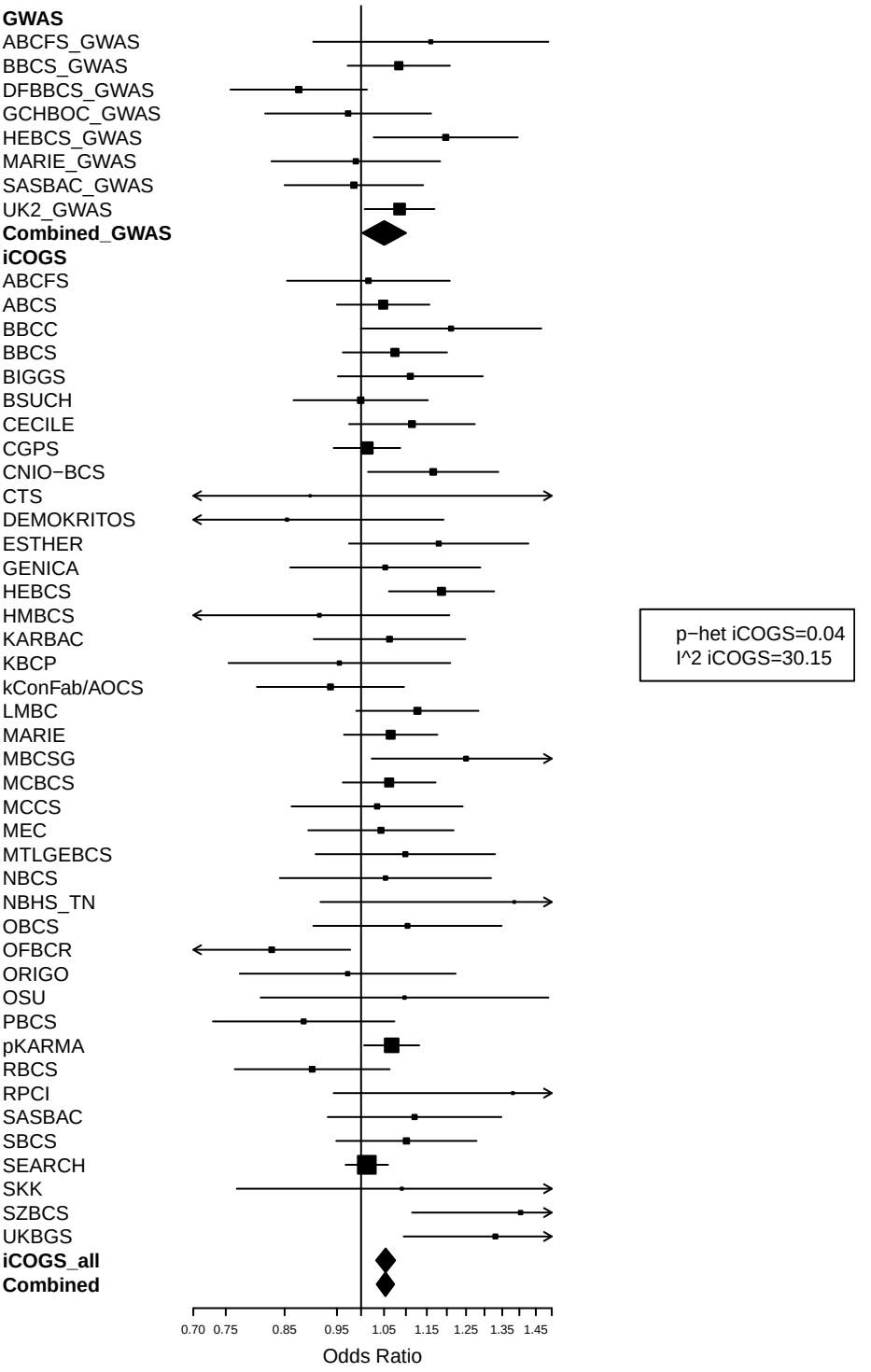
Odds Ratio

**rs9257408**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BBCS_GWAS
DFBBCS_GWAS
GCHBOC_GWAS
HEBCS_GWAS
MARIE_GWAS
SASBAC_GWAS
UK2_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
CNIO−BCS
CTS
DEMOKRITOS
ESTHER
GENICA
HEBCS
HMBCS
KARBAC
KBCP
kConFab/AOCS
LMBC
MARIE
MBCSG
MCBCS
MCCS
MEC
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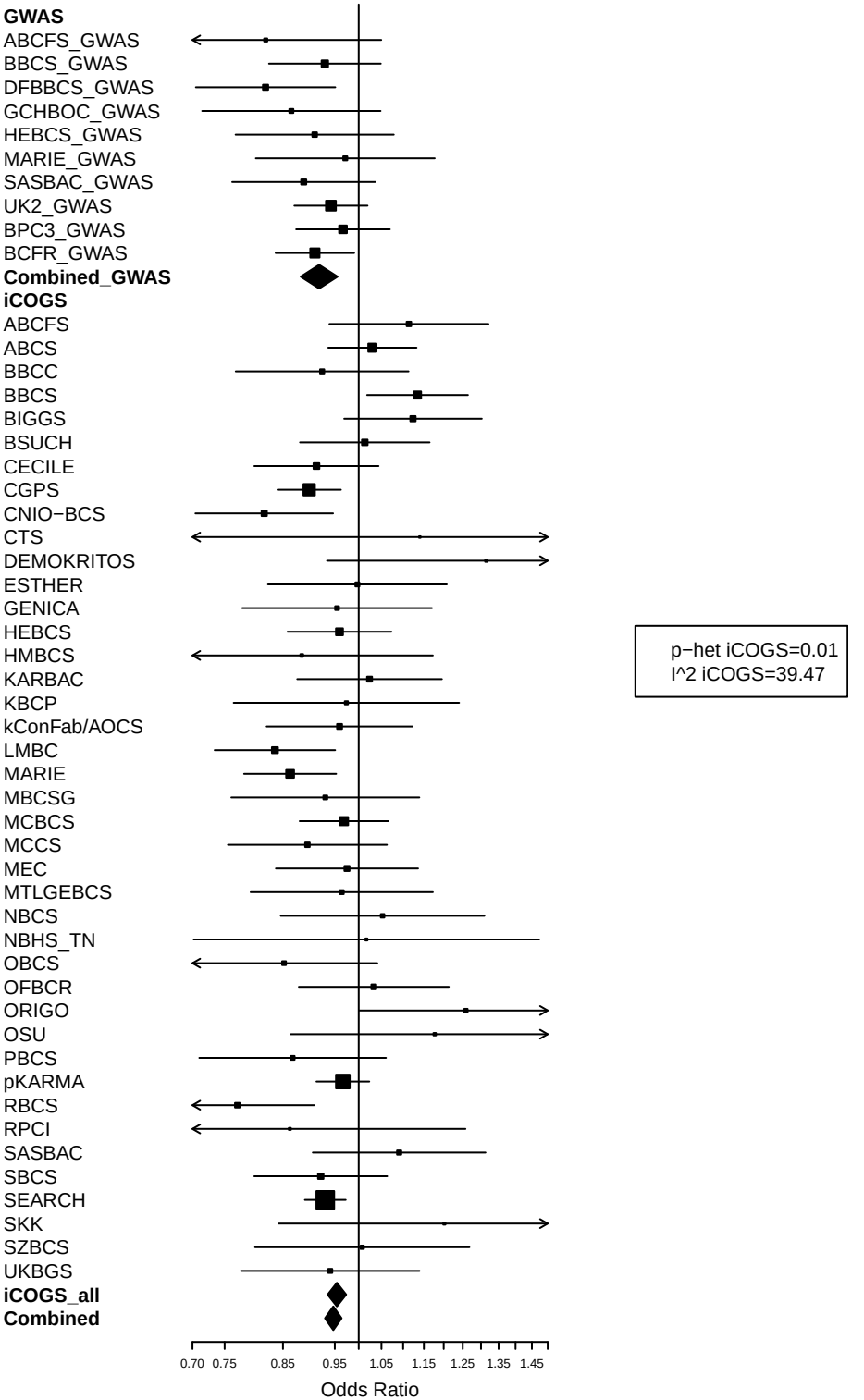
NBCS
NBHS_TN
OBCS
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
p−het iCOGS=0.04
I^2 iCOGS=30.15

# rs4593472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HEBCS_GWAS
MARIE_GWAS
SASBAC_GWAS
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BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
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CTS
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GENICA
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HMBCS
KARBAC
KBCP
kConFab/AOCS
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MARIE
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OBCS
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ORIGO
OSU
PBCS
pKARMA
RBCS
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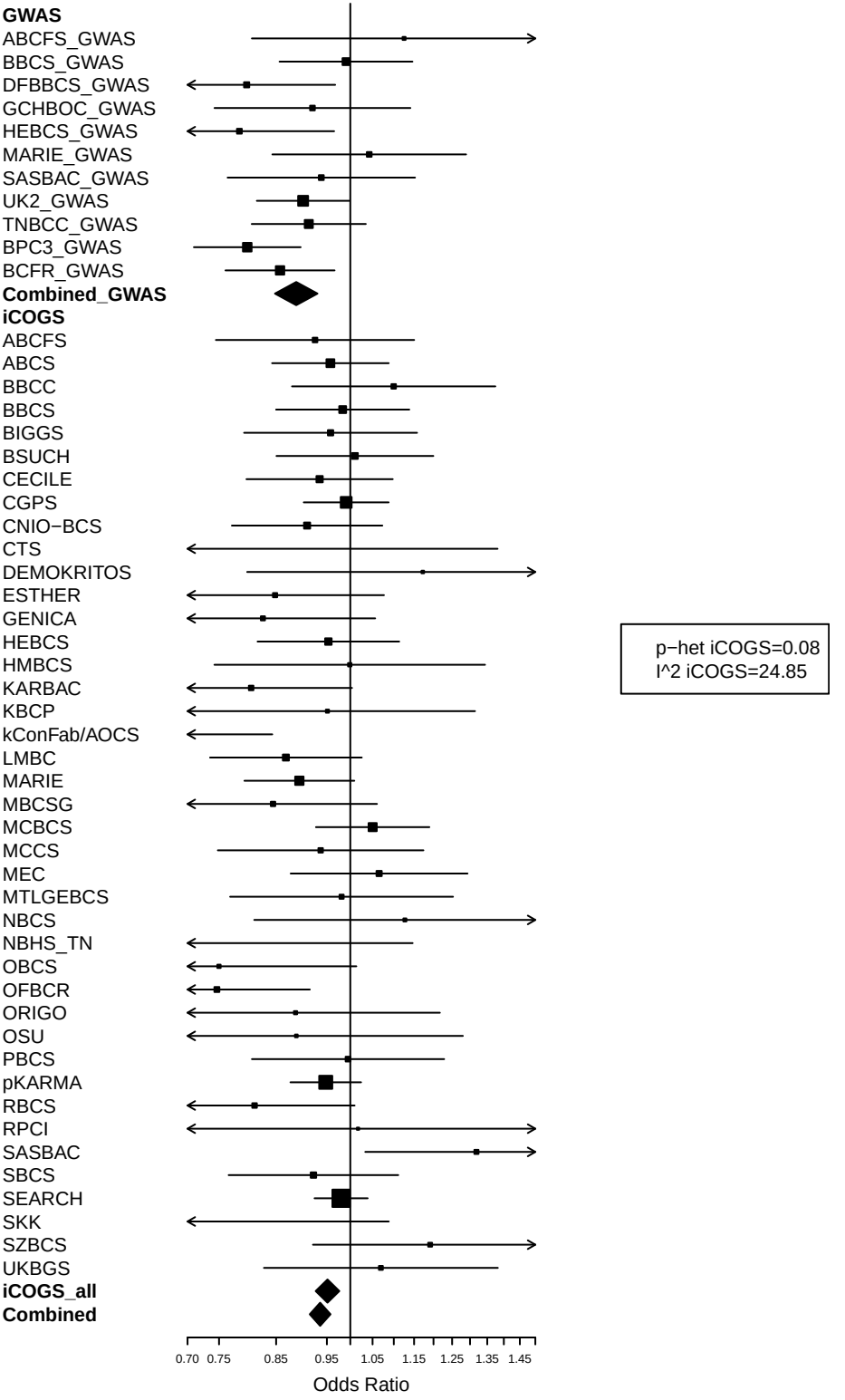
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
p−het iCOGS=0.01
I^2 iCOGS=39.47

# rs13365225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BBCS_GWAS
DFBBCS_GWAS
GCHBOC_GWAS
HEBCS_GWAS
MARIE_GWAS
SASBAC_GWAS
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TNBCC_GWAS
BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
CNIO−BCS
CTS
DEMOKRITOS
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OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
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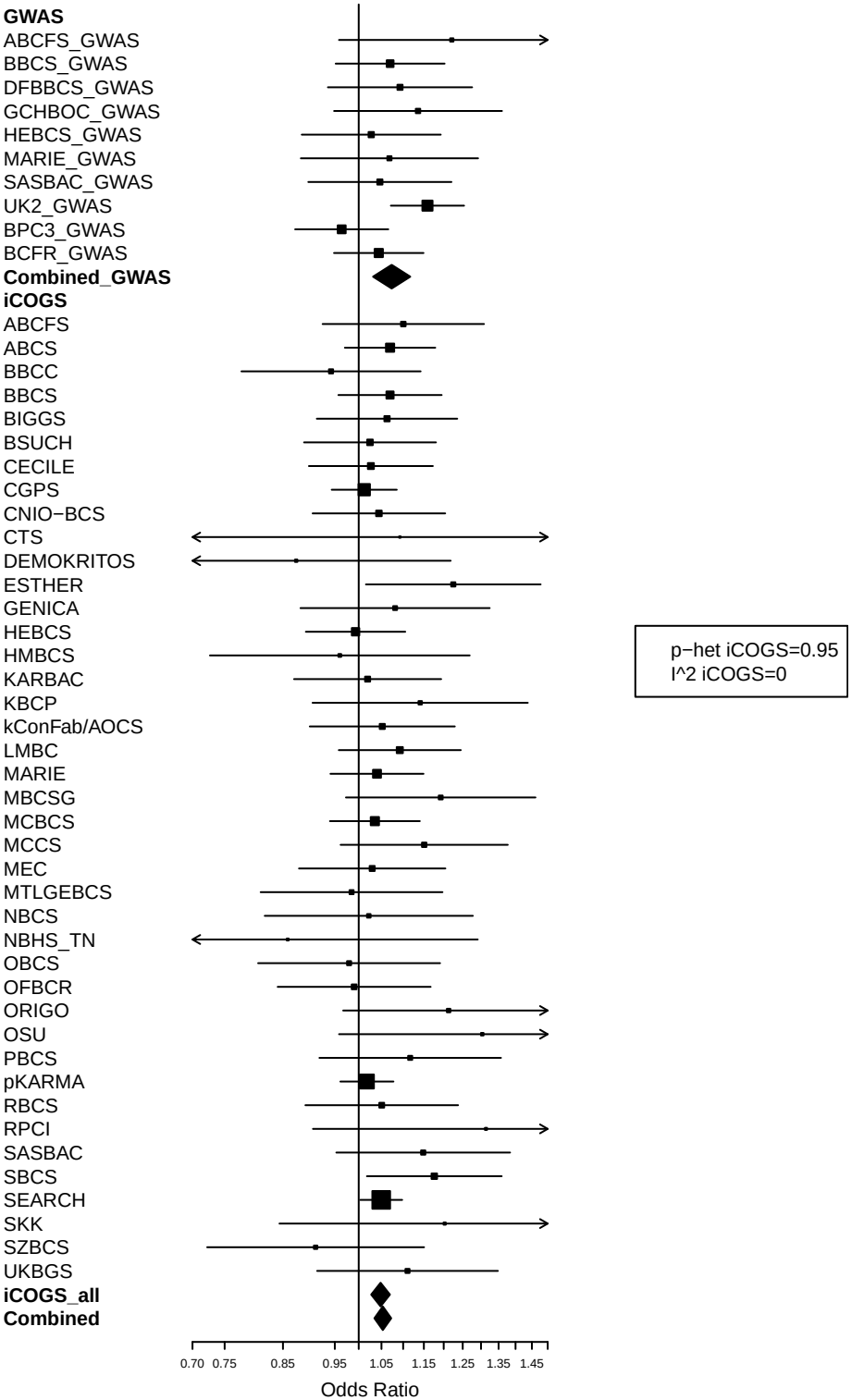
I^2 iCOGS=24.85

**rs13267382**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SASBAC_GWAS
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BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
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LMBC
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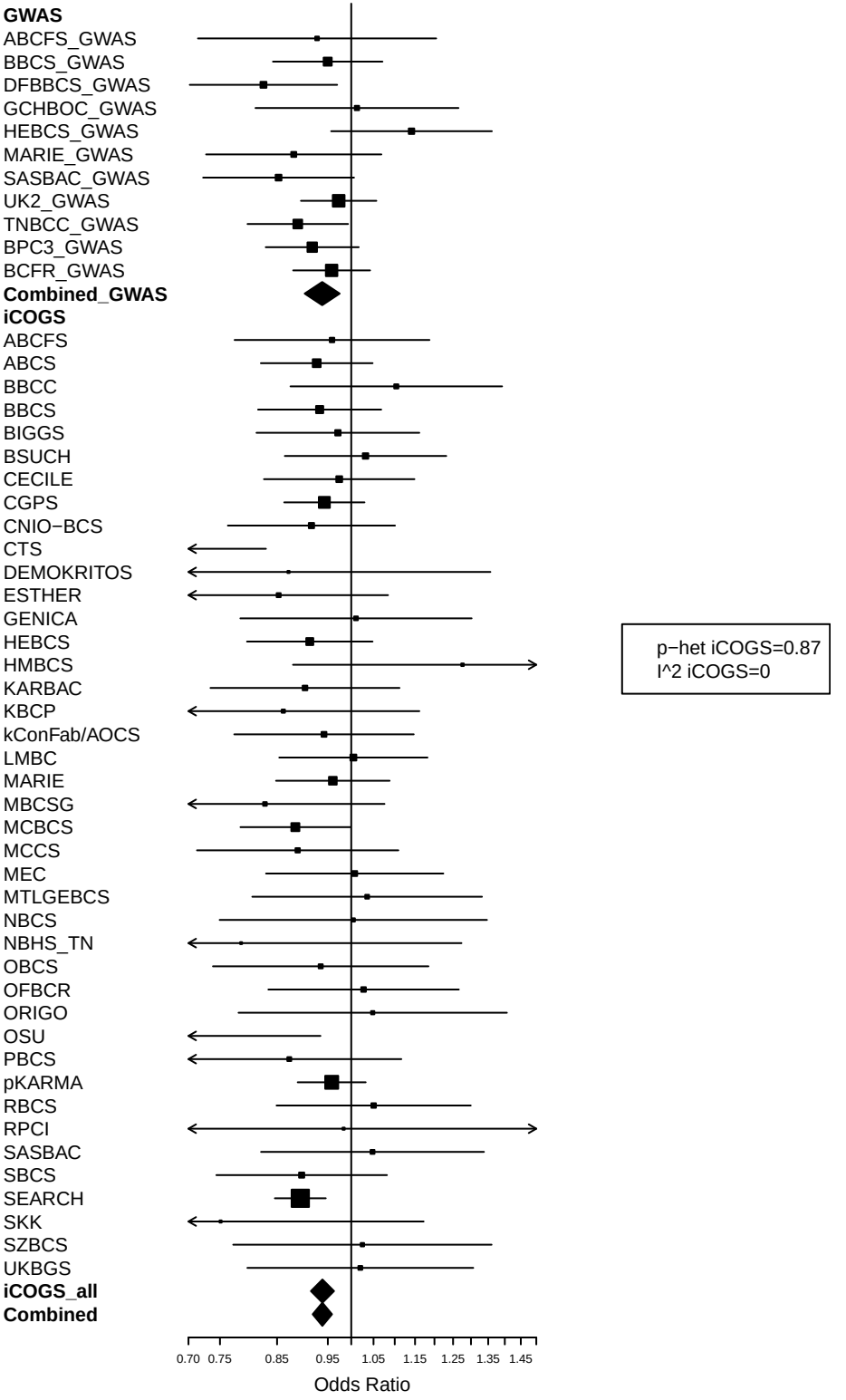
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
p−het iCOGS=0.95
I^2 iCOGS=0

# rs11627032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BBCS_GWAS
DFBBCS_GWAS
GCHBOC_GWAS
HEBCS_GWAS
MARIE_GWAS
SASBAC_GWAS
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TNBCC_GWAS
BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
CNIO−BCS
CTS
DEMOKRITOS
ESTHER
GENICA
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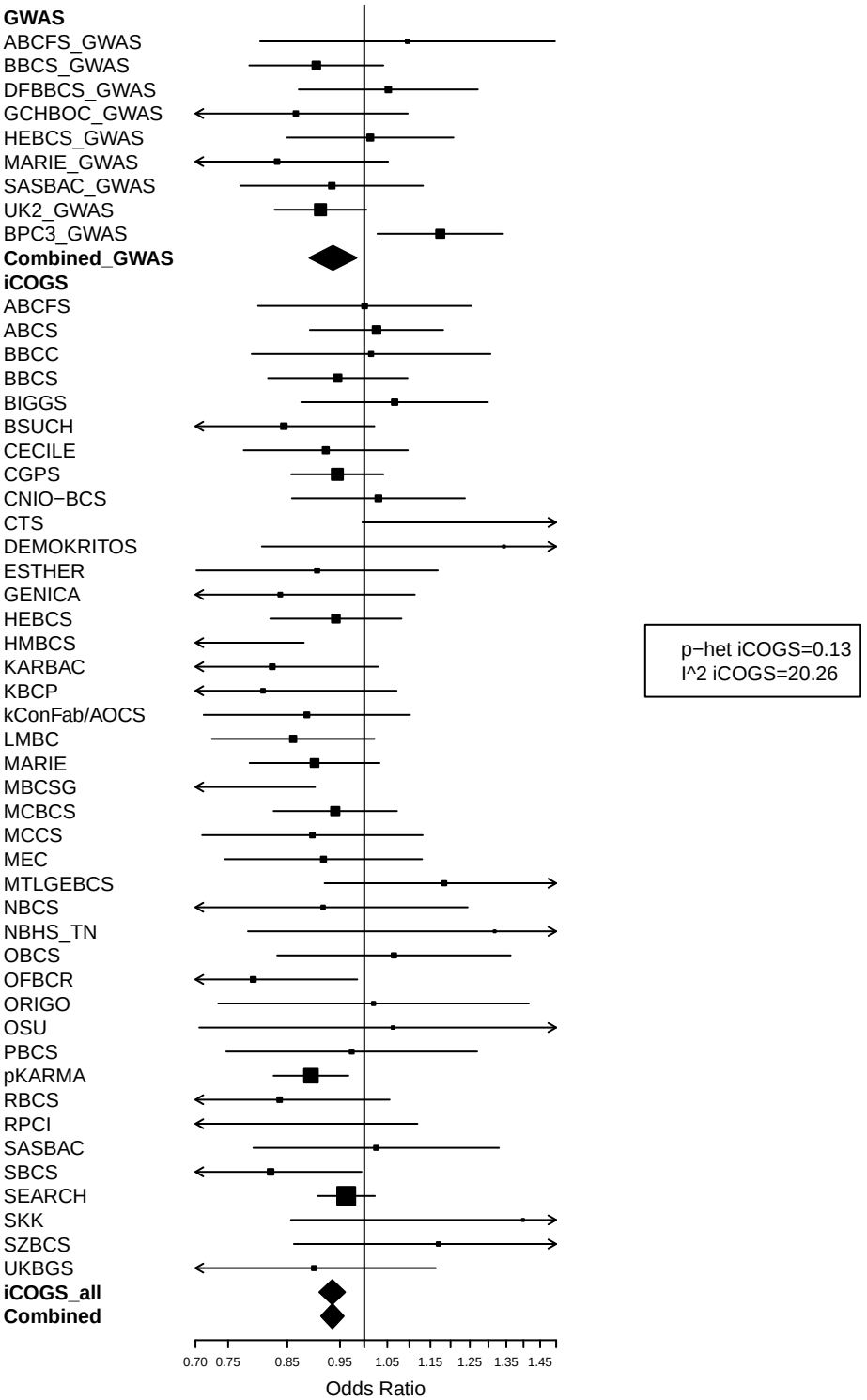
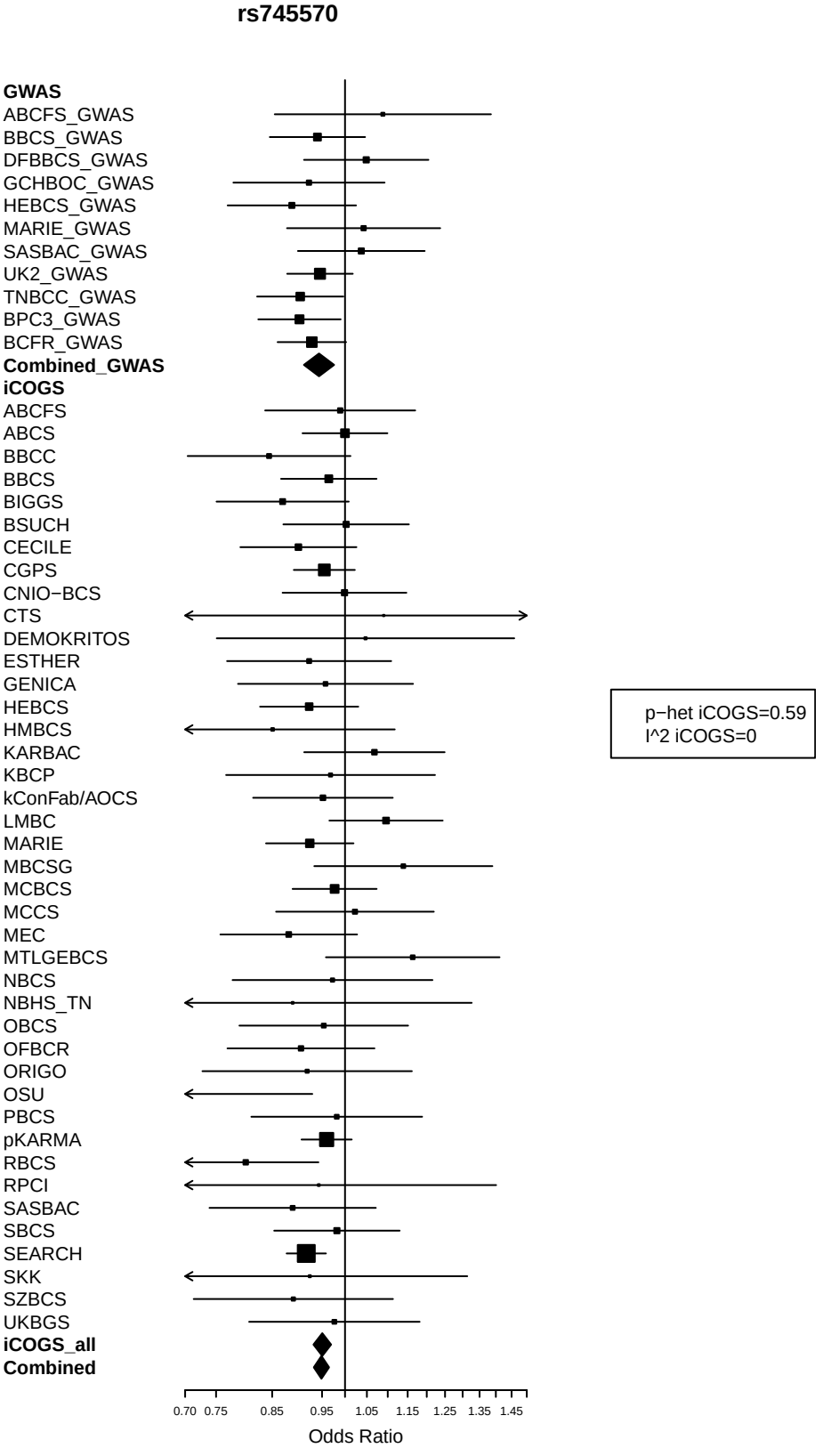
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
p−het iCOGS=0.87
I^2 iCOGS=0

**chr17:29230520:D**

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BBCS_GWAS
DFBBCS_GWAS
GCHBOC_GWAS
HEBCS_GWAS
MARIE_GWAS
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UK2_GWAS
TNBCC_GWAS
BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
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CTS
DEMOKRITOS
ESTHER
GENICA
HEBCS
HMBCS
KARBAC
KBCP
kConFab/AOCS
LMBC
MARIE
MBCSG
MCBCS
MCCS
MEC
MTLGEBCS
NBCS
NBHS_TN
OBCS
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
p−het iCOGS=0.59
I^2 iCOGS=0
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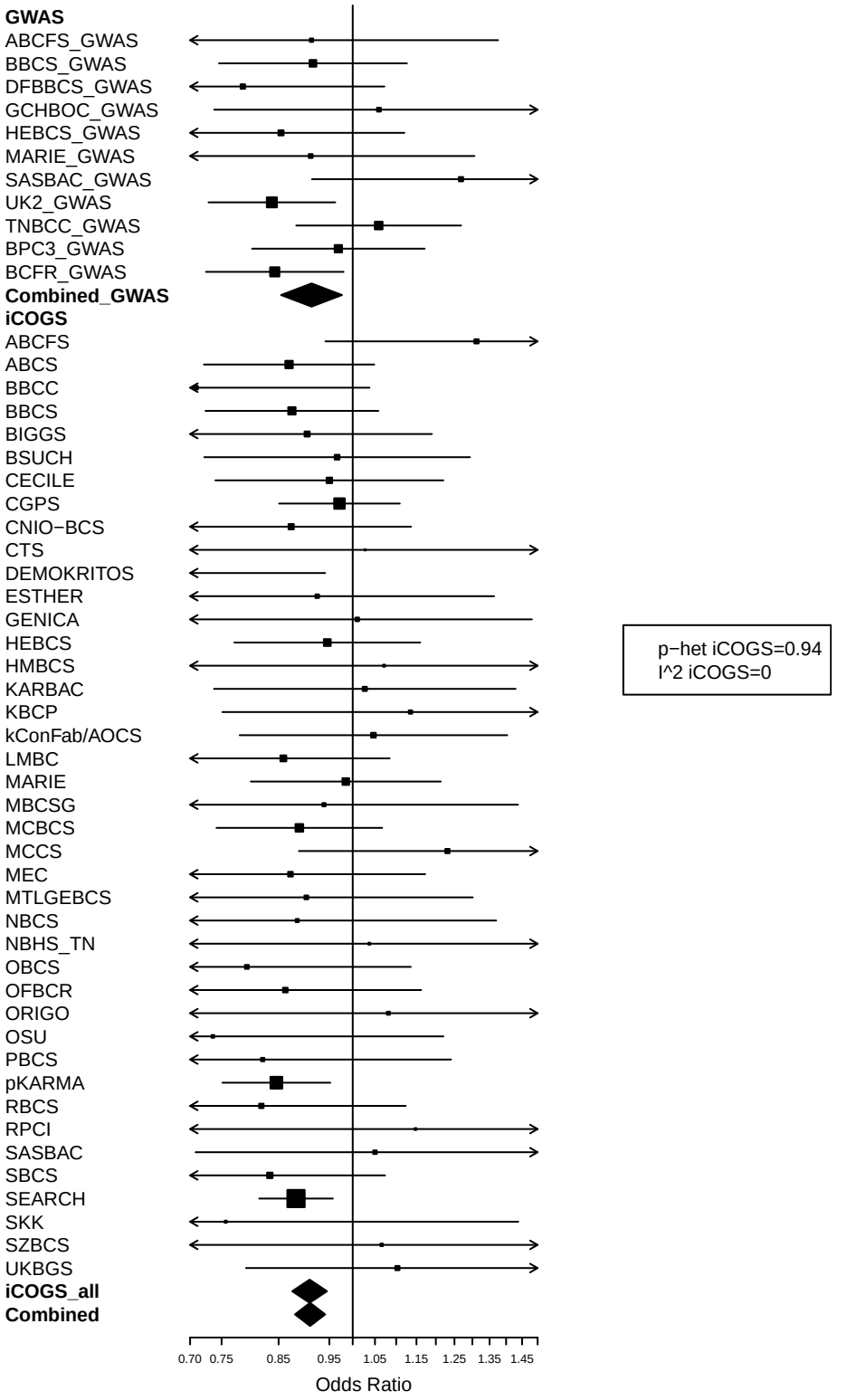
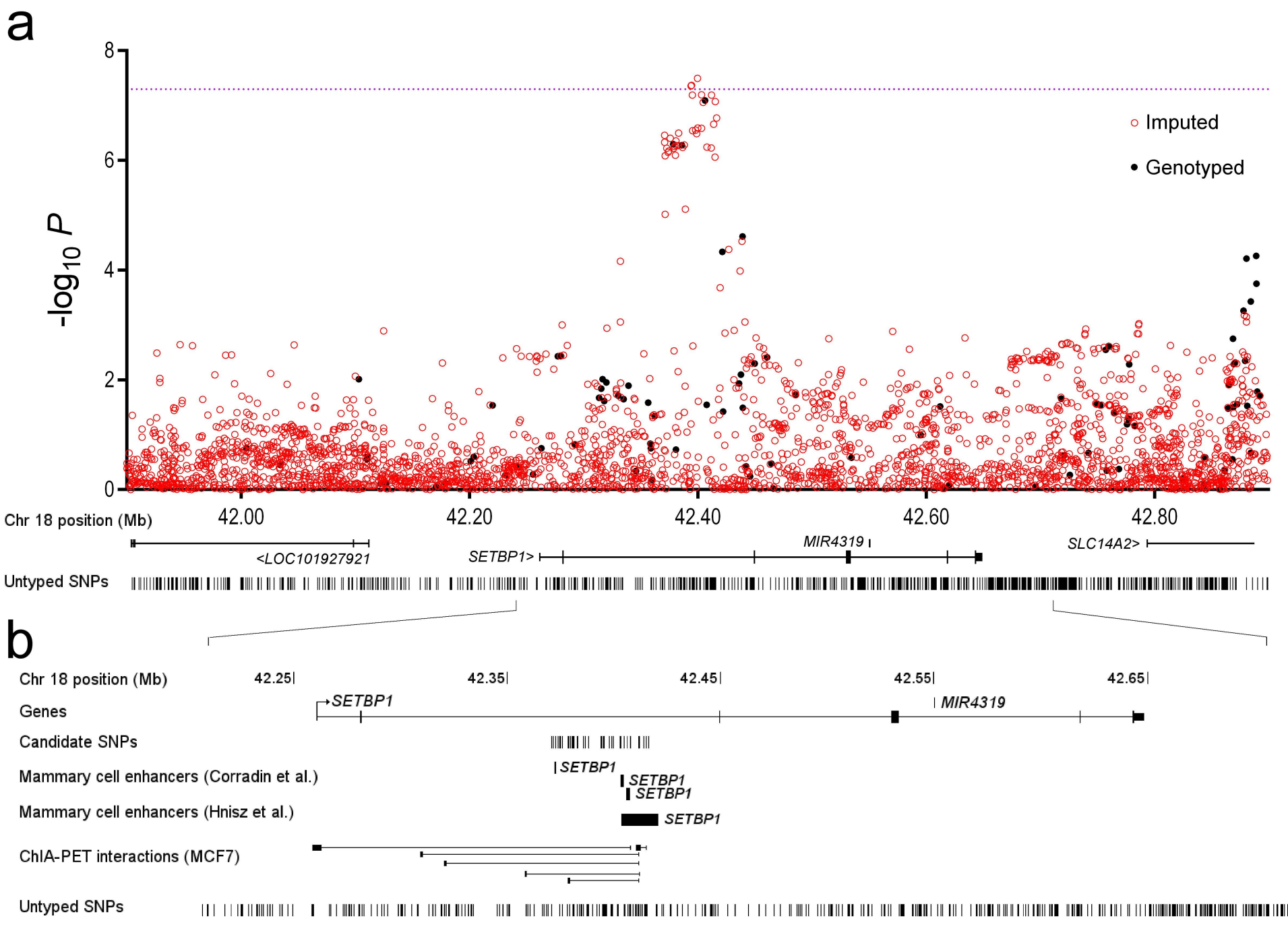
Odds Ratio

# rs6507583


GWAS
ABCFS_GWAS
BBCS_GWAS
DFBBCS_GWAS
GCHBOC_GWAS
HEBCS_GWAS
MARIE_GWAS
SASBAC_GWAS
UK2_GWAS
TNBCC_GWAS
BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
CNIO−BCS
CTS
DEMOKRITOS
ESTHER
GENICA
HEBCS
HMBCS
KARBAC
KBCP
kConFab/AOCS
LMBC
MARIE
MBCSG
MCBCS
MCCS
MEC
MTLGEBCS
NBCS
NBHS_TN
OBCS
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
p−het iCOGS=0.94
I^2 iCOGS=0

**Supplementary Figure 5:** The chromosome 18 locus tagged by rs6507583 **a)** The Manhattan Plot displays the strength of genetic association ($-\log_{10}$ P) versus chromosomal position (Mb), where each dot presents a genotyped (solid black dot) or imputed (red circle) SNP (in the iCOGS stage). The purple horizontal line represents the threshold for genome-wide significance ($P=5x10^{-8}$). Gene structures are depicted as well as the location of SNPs with MAF>0.01 which were neither imputed reliably nor genotyped. **b)** Mammary cell enhancer locations as defined in Corradin et al.[33], and Hnisz et al.[34], are shown where elements overlapping the best associated SNPs are labelled with their predicted target genes. A subset of ChiA-PET interactions in MCF7 cells (mediated by either RNApolII or ERa) between enhancers and their target gene promoters are also shown.


a
8
6
4
2
0
-log10 P
Imputed
Genotyped
Chr 18 position (Mb)
42.00
42.20
42.40
42.60
42.80
<LOC101927921
SETBP1>
MIR4319
SLC14A2>
Untyped SNPs
b
Chr 18 position (Mb)
42.25
42.35
42.45
42.55
42.65
Genes
SETBP1
MIR4319
Candidate SNPs
Mammary cell enhancers (Corradin et al.)
SETBP1
SETBP1
SETBP1
Mammary cell enhancers (Hnisz et al.)
SETBP1
ChIA-PET interactions (MCF7)
Untyped SNPs

**Supplementary Figure 6:** Manhattan plots of association for the eQTL results (chromosome 5, b37: 80,928,261-81,928,2611) in all breast cancer tumours, ER+, ER- tumours and normal from the TCGA data. The bottom plot represents the breast cancer meta-analysis risk results.

RPS23

All tumours

ER+ tumours

ER- tumours

Normals

GWAS

Gene

$-\log_{10}(P)$

Probe
A_23_P253519
AK092335_1_1335
AK092335_1_1696

81000000
81250000
81500000
81750000
82000000

**Supplementary Table 1.** Studies contributing to the analysis.

**Supplementary Table 1a**. BCAC Genome-Wide Association Studies.

| **Study**[1] | **Country** | **Cases**[1,2] | **Controls**[1,2] | **ER+/ER- cases**[1,2] | **Genotyping Platform** |
|---|---|---|---|---|---|
| ABCFS/kConFab | Australia | 282 | 285 | 88/72 (72) | Illumina 610k |
| BBCS[4] | U.K. | 1609 | 1224 | - | Illumina 370k (cases)/ Illumina 1.2M (controls) |
| DFBBCS[5] | Netherlands | 464 | 3255 | - | Illumina 610k (cases) /Illumina 550k (controls) |
| GC-HBOC[6] | Germany | 634 | 477 | - | Affymetrix 5.0k(cases) /Affymetrix 6.0k (controls) |
| GWAS_UK2[4] | U.K. | 3628 | 2663 | 361/160 (160) | Illumina 670k (cases)/Illumina 1.2M (controls) |
| HEBCS[7] | Finland | 726 | 1012 | 522/229 (145) | Illumina 550k+ 610k (cases)/ Illumina 370k (controls) |
| MARIE[6] | Germany | 652 | 470 | 567/132 (76) | Illumina 370k (cases) /Illumina 550k (controls) |
| SASBAC | Sweden | 790 | 756 | 481/109 (109) | Illumina 317k+240k (cases) /Illumina 550k (controls) |

[1]For further details see [3].

[2] Sample numbers after quality control exclusions.

[3]Numbers in brackets are numbers of ER-cases after elimination of duplicates with TNBCC.

[4] Controls from Welcome Trust Case-Control Consortium.

[5] Controls from Rotterdam Study.

[6] Controls from KORA.

[7] Controls from NordicDB.

**Supplementary Table 1b** Studies contributing to the BPC3 GWAS

| Study[1] | Country | Cases | Controls | ER+/ER- cases[2] |
|---|---|---|---|---|
| CPS-II | USA | 293 | 295 | 0/293 |
| EPIC | Europe | 511 | 500 | 0/511 |
| MEC | USA | 86 | 101 | 0/86 |
| NHS2 | USA | 76 | 374 | 0/76 |
| PBCS | Poland | 543 | 511 | 0/543 |
| PLCO | USA | 255 | 340 | 0/255 |
| NHS | USA | 234 | 184 | 0/234 |

[1] For further details see [4,5].

[2] Cases selected to be ER-negative

**Supplementary table 1c:** Studies contributing to the Early-onset Breast Cancer GWAS (EBCG).

| Site[1] | Country | Cases | Controls | ER+/ER- cases |
|---|---|---|---|---|
| BCFR (AUS) | Australia | 593 | 250 | 368/176 |
| BCFR (NCA) | USA | 204 | 156 | 130/48 |
| BCFR (Ontario) | Canada | 668 | 395 | 404/185 |
| GESBC | Germany | 553 | 1,071 | 288/179 |
| LI | US | 225 | 275 | 112/53 |
| Seattle | US | 297 | 328 | 219/72 |
| USC | US | 983 | - | 662/198 |
| CCFR | US | - | 227 | - |

[1] For further details see [6].

**Supplementary Table 1d:** Studies contributing to the TNBCC GWAS

| **Study**[1] | **Country** | **Cases** | **Controls**[2] | **ER+/ER- cases**[3] |
|---|---|---|---|---|
| ABCTB | Australia | 144 | 0 | 0/144 |
| MCCS | Australia | 39 | 0 | 0/39 |
| QIMR | Australia | 0 | 650 | - |
| BBCC | Germany | 218 | 0 | 0/218 |
| GENICA | Germany | 59 | 0 | 0/59 |
| MARIE | Germany | 198 | 0 | 0/198 |
| KORA | Germany | 0 | 215 | - |
| DFCI | USA | 246 | 0 | 0/246 |
| FCCC | USA | 120 | 0 | 0/120 |
| MCBCS | USA | 147 | 0 | 0/147 |
| CGEMS | USA | 0 | 947 | - |
| POSH | UK | 266 | 0 | 0/266 |
| SBCS | UK | 42 | 0 | 0/42 |
| WTCCC | UK | 0 | 1368 | - |

[1] For further details see [4,7,8].

[2] TNBCC used external controls, drawn from population-based studies from the same countries as the cases.

[3] Cases were selected to be ER-negative, PR-negative and HER2-negative.

**Supplementary Table 1e**: Studies contributing to the iCOGS analysis.

| Study[1] | Country | Cases | Controls | ER+/ER- Cases |
|---|---|---|---|---|
| ABCFS | Australia | 643 | 551 | 383/204 |
| ABCS | Netherlands | 2029 | 1815 | 768/282 |
| BBCC | Germany | 548 | 458 | 460/67 |
| BBCS | U.K. | 1507 | 1397 | 493/108 |
| BIGGS | Ireland | 836 | 719 | 495/154 |
| BSUCH | Germany | 848 | 954 | 548/157 |
| CECILE | France | 1019 | 999 | 797/144 |
| CGPS | Denmark | 2948 | 4534 | 1919/357 |
| CNIO-BCS | Spain | 902 | 876 | 242/88 |
| CTS | U.S.A. | 68 | 71 | 0/68 |
| DEMOKRITOS | Greece | 413 | 95 | 0/413 |
| ESTHER | Germany | 478 | 502 | 304/98 |
| GENICA | Germany | 449 | 427 | 327/104 |
| HEBCS | Finland | 1658 | 1233 | 1292/235 |
| HMBCS | Belarus | 690 | 130 | 37/8 |
| KARBAC | Sweden | 722 | 662 | 338/63 |
| KBCP | Finland | 441 | 250 | 300/97 |
| kConFab/AOCS | Australia | 575 | 897 | 152/55 |
| LMBC | Belgium | 2671 | 1388 | 2071/378 |
| MARIE | Germany | 1743 | 1788 | 1328/346 |
| MBCSG | Italy | 488 | 400 | 149/42 |
| MCBCS | U.S.A. | 1836 | 1931 | 1486/269 |
| MCCS | Australia | 604 | 511 | 351/110 |
| MEC | U.S.A. | 731 | 741 | 415/87 |
| MTLGEBCS | Canada | 489 | 436 | 421/64 |
| NBCS | Norway | 908 | 217 | 620/201 |
| NBHS_TN | U.S.A. | 125 | 118 | 0/125 |
| OBCS | Finland | 505 | 414 | 405/100 |
| OFBCR | Canada | 1175 | 511 | 629/269 |
| ORIGO | Netherlands | 354 | 327 | 208/70 |
| OSU | U.S.A. | 207 | 203 | 0/207 |
| PBCS | Poland | 519 | 424 | 519/0 |
| pKARMA | Sweden | 5429 | 5568 | 3670/701 |
| RBCS | Netherlands | 599 | 699 | 323/124 |
| RPCI | U.S.A | 136 | 126 | 0/136 |
| SASBAC | Sweden | 397 | 661 | 198/43 |
| SBCS | U.K. | 832 | 848 | 376/98 |
| SEARCH | U.K. | 9293 | 8068 | 5146/1173 |
| SKK | Germany | 135 | 168 | 0/135 |
| SZBCS | Poland | 365 | 315 | 165/60 |
| UKBGS | U.K. | 470 | 470 | 95/22 |

[1] For further details see [3].

**Supplementary Table 2**: Number (proportion) of variants reaching imputation $r^2$ (calculated by the info score IMPUTE2) in iCOGS and UK2 GWAS.

| Study | #samples | MAF | #variants (proportion) | $r^2$>0.3 | $r^2$>0.5 | $r^2$>0.8 | $r^2$>0.9 |
|---|---|---|---|---|---|---|---|
| **iCOGS** | 91,197 | All | 17,434,450 (1.00) | 15,703,697 (0.90) | 10,325,641 (0.59) | 4,784,120 (0.27) | 3,145,739 (0.18) |
| | | >=0.05 | 6,761,363 (1.00) | 6,693,225 (0.99) | 5,950,307 (0.88) | 3,614,230 (0.53) | 2,527,392 (0.37) |
| | | <0.05 | 10,673,087 (1.00) | 9,010,472 (0.84) | 4,375,334 (0.41) | 1,169,890 (0.11) | 618,347 (0.06) |
| **UK2** | 7,209 | All | 17,434,450 (1.00) | 15,645,874 (0.90) | 13,246,754 (0.76) | 9,205,844 (0.53) | 7,739,369 (0.45) |
| | | >=0.05 | 6,761,363 (1.00) | 6,745,439 (0.998) | 6,673,659 (0.987) | 6,197,337 (0.92) | 5,741,475 (0.85) |
| | | <0.05 | 10,673,087 (1.00) | 8,900,435 (0.85) | 6,573,095 (0.62) | 3,008,507 (0.28) | 1,997,894 (0.19) |

**Supplementary Table 3.** Association results for 79 breast cancer susceptibility loci previously reported in studies of women of European ancestry.

**Supplementary table 3a.** Association results for overall breast cancer.

| SNP[1] | Chr[2] | Position[3] | Alleles[4] | MAF[5] GWAS | GWAS OR (95%CI)[6] | GWAS *P*[7] | MAF[5] iCOGS | $r^2$ iCOGS[8] | iCOGS OR (95%CI)[6] | iCOGS *P*[7] | Combined *P*[9] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs616488 | 1 | 10566215 | A/G | 0.34 | 0.94(0.91-0.98) | 0.00113 | 0.33 | 1 | 0.94(0.92-0.96) | $8.75x10^{-09}$ | $3.82x10^{-11}$ |
| rs11552449 | 1 | 114448389 | C/T | 0.17 | 1.08(1.03-1.13) | 0.00115 | 0.16 | 1 | 1.07(1.04-1.09) | $5.98x10^{-07}$ | $2.75x10^{-09}$ |
| rs11249433 | 1 | 121280613 | A/G | 0.42 | 1.11(1.07-1.16) | $6.71x10^{-09}$ | 0.4 | 1 | 1.09(1.07-1.12) | $4.43x10^{-20}$ | $2.66x10^{-27}$ |
| rs6678914 | 1 | 202187176 | G/A | 0.42 | 0.94(0.91-0.98) | 0.000942 | 0.41 | 1 | 1.00(0.98-1.02) | 0.712 | 0.050 |
| rs4245739 | 1 | 204518842 | A/C | 0.27 | 1.03(0.99-1.07) | 0.193 | 0.26 | 1 | 1.03(1.01-1.05) | 0.00503 | 0.00206 |
| rs12710696 | 2 | 19320803 | C/T | 0.36 | 1.07(1.04-1.11) | $4.57x10^{-05}$ | 0.36 | 1 | 1.04(1.02-1.06) | 0.000481 | $4.36x10^{-07}$ |
| rs4849887 | 2 | 121245122 | C/T | 0.1 | 0.91(0.86-0.96) | 0.00107 | 0.1 | 1 | 0.91(0.88-0.94) | $4.89x10^{-09}$ | $2.04x10^{-11}$ |
| rs2016394 | 2 | 172972971 | G/A | 0.47 | 0.99(0.96-1.02) | 0.512 | 0.48 | 1 | 0.95(0.94-0.97) | $1.90x10^{-06}$ | $8.11x10^{-06}$ |
| *rs1550623** | *2* | *174212894* | *A/G* | *0.16* | *0.94(0.9-0.99)* | *0.0146* | *0.16* | *1* | *0.95(0.92-0.97)* | $2.88x10^{-05}$ | $1.27x10^{-06}$ |
| *rs1045485** | *2* | *202149589* | *G/C* | *0.13* | *0.91(0.87-0.96)* | *0.000612* | *0.13* | *1* | *0.97(0.94-1)* | *0.0463* | *0.000689* |
| rs13387042 | 2 | 217905832 | A/G | 0.49 | 0.87(0.84-0.9) | $1.27x10^{-16}$ | 0.49 | 1 | 0.88(0.86-0.9) | $8.91x10^{-41}$ | $1.15x10^{-55}$ |
| rs16857609 | 2 | 218296508 | C/T | 0.26 | 1.08(1.04-1.12) | $3.08x10^{-05}$ | 0.26 | 1 | 1.08(1.06-1.11) | $9.48x10^{-1}$ | $1.41x10^{-17}$ |
| rs6762644 | 3 | 4742276 | A/G | 0.39 | 1.04(1.01-1.08) | 0.02 | 0.4 | 1 | 1.07(1.05-1.09) | $6.28x10^{-11}$ | $8.58x10^{-12}$ |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs4973768 | 3 | 27416013 | C/T | 0.47 | 1.11(1.07-1.15) | $7.45x10^{-10}$ | 0.47 | 1 | 1.1(1.08-1.12) | $4.65x10^{-22}$ | $2.68x10^{-30}$ |
| rs12493607 | 3 | 30682939 | G/C | 0.35 | 1.04(1-1.07) | 0.0385 | 0.34 | 1 | 1.06(1.04-1.08) | $7.00x10^{-08}$ | $1.13x10^{-08}$ |
| rs1053338 | 3 | 63967900 | A/G | 0.13 | 1.06(1.01-1.12) | 0.016 | 0.13 | 1 | 1.08(1.05-1.11) | $1.65x10^{-07}$ | $9.08x10^{-9}$ |
| rs9790517 | 4 | 106084778 | C/T | 0.22 | 1.09(1.05-1.14) | $1.38x10^{-05}$ | 0.22 | 1 | 1.05(1.03-1.08) | $6.85x10^{-06}$ | $1.43x10^{-09}$ |
| rs6828523 | 4 | 175846426 | C/A | 0.12 | 0.9(0.85-0.95) | $9.02x10^{-05}$ | 0.12 | 1 | 0.9(0.87-0.93) | $2.77x10^{-12}$ | $1.14Ex10^{-15}$ |
| rs10069690 | 5 | 1279790 | C/T | 0.26 | 1.04(0.98-1.1) | 0.219 | 0.26 | 1 | 1.06(1.04-1.09) | $1.70x10^{-08}$ | $1.10x10^{-08}$ |
| *rs7726159** | *5* | *1282319* | *C/A* | *0.35* | *1(0.95-1.05)* | *0.956* | *0.34* | *1* | *1.04(1.02-1.06)* | *$3.65x10^{-05}$* | *0.000174* |
| rs2736108 | 5 | 1297488 | C/T | 0.27 | 0.94(0.89-0.99) | 0.0137 | 0.29 | 1 | 0.94(0.92-0.96) | $5.47x10^{-08}$ | $2.44x10^{-09}$ |
| rs10941679 | 5 | 44706498 | A/G | 0.25 | 1.13(1.08-1.18) | $2.31x10^{-07}$ | 0.25 | 1 | 1.12(1.1-1.15) | $3.20x10^{-26}$ | $4.50x10^{-32}$ |
| rs889312 | 5 | 56031884 | A/C | 0.28 | 1.15(1.11-1.2) | $2.26x10^{-14}$ | 0.28 | 1 | 1.12(1.1-1.15) | $2.87x10^{-27}$ | $1.19x10^{-39}$ |
| rs10472076 | 5 | 58184061 | T/C | 0.36 | 1.06(1.02-1.09) | 0.00275 | 0.38 | 1 | 1.05(1.03-1.07) | $1.82x10^{-06}$ | $1.84x10^{-08}$ |
| rs1353747 | 5 | 58337481 | T/G | 0.1 | 0.92(0.87-0.98) | 0.00698 | 0.1 | 1 | 0.92(0.89-0.95) | $1.38x10^{-06}$ | $3.19x10^{-08}$ |
| rs1432679 | 5 | 158244083 | T/C | 0.43 | 1.08(1.04-1.11) | $2.20x10^{-05}$ | 0.43 | 1 | 1.07(1.05-1.09) | $3.60x10^{-12}$ | $3.93x10^{-16}$ |
| *rs11242675** | *6* | *1318878* | *T/C* | *0.38* | *0.95(0.92-0.98)* | *0.00362* | *0.38* | *1* | *0.96(0.94-0.98)* | *$1.07x10^{-05}$* | *$1.40x10^{-07}$* |
| rs204247 | 6 | 13722523 | A/G | 0.44 | 1.06(1.03-1.1) | 0.000326 | 0.44 | 1 | 1.05(1.03-1.07) | $2.71Ex10^{-07}$ | $4.18x10^{-10}$ |
| rs17529111 | 6 | 82128386 | T/C | 0.21 | 1.1(1.05-1.15) | $3.50x10^{-05}$ | 0.22 | 1 | 1.06(1.04-1.08) | $4.90x10^{-07}$ | $2.03x10^{-10}$ |
| rs12662670 | 6 | 151918856 | T/G | 0.08 | 1.22(1.14-1.29) | $6.22x10^{-10}$ | 0.07 | 1 | 1.17(1.13-1.22) | $1.03x10^{-18}$ | $6.80x10^{-27}$ |
| rs2046210 | 6 | 151948366 | G/A | 0.35 | 1.13(1.09-1.17) | $3.61x10^{-12}$ | 0.34 | 1 | 1.08(1.06-1.1) | $2.13x10^{-14}$ | $5.94x10^{-24}$ |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *rs6964587** | *7* | *91630620* | *G/T* | *0.39* | *1.03(0.99-1.06)* | *0.11* | *0.39* | *1* | *1.05(1.03-1.07)* | *1.26x10$^{-06}$* | *4.90x10$^{-07}$* |
| rs720475 | 7 | 144074929 | G/A | 0.24 | 0.95(0.91-0.99) | 0.00834 | 0.25 | 1 | 0.94(0.92-0.96) | 1.23x10$^{-08}$ | 3.85x10$^{-10}$ |
| rs9693444 | 8 | 29509616 | C/A | 0.32 | 1.06(1.02-1.1) | 0.00209 | 0.32 | 1 | 1.07(1.05-1.09) | 1.09x10$^{-10}$ | 1.00x10$^{-12}$ |
| rs6472903 | 8 | 76230301 | T/G | 0.17 | 0.91(0.87-0.96) | 9.46x10$^{-05}$ | 0.18 | 1 | 0.91(0.89-0.93) | 2.74x10$^{-13}$ | 1.21x10$^{-16}$ |
| rs2943559 | 8 | 76417937 | A/G | 0.07 | 1.19(1.11-1.27) | 1.36x10$^{-07}$ | 0.07 | 1 | 1.13(1.09-1.17) | 6.81x10$^{-11}$ | 1.41x10$^{-16}$ |
| rs13281615 | 8 | 128355618 | A/G | 0.41 | 1.12(1.08-1.15) | 1.91x10$^{-10}$ | 0.4 | 1 | 1.1(1.08-1.12) | 3.26x10$^{-22}$ | 5.52x10$^{-31}$ |
| rs11780156 | 8 | 129194641 | C/T | 0.17 | 1.08(1.03-1.13) | 0.000763 | 0.16 | 1 | 1.07(1.04-1.09) | 7.67x10$^{-07}$ | 2.42x10$^{-09}$ |
| rs1011970 | 9 | 22062134 | G/T | 0.17 | 1.11(1.06-1.16) | 6.57x10$^{-06}$ | 0.17 | 1 | 1.06(1.03-1.08) | 2.68x10$^{-05}$ | 4.02x10$^{-09}$ |
| rs10759243 | 9 | 110306115 | C/A | 0.27 | 1.08(1.03-1.12) | 0.000708 | 0.29 | 1 | 1.05(1.03-1.08) | 6.92x10$^{-07}$ | 2.69x10$^{-09}$ |
| rs865686 | 9 | 110888478 | T/G | 0.37 | 0.91(0.88-0.94) | 1.96x10$^{-08}$ | 0.38 | 1 | 0.9(0.88-0.92) | 4.49x10$^{-27}$ | 6.42x10$^{-34}$ |
| *rs2380205** | *10* | *5886734* | *C/T* | *0.44* | *0.95(0.92-0.98)* | *0.00147* | *0.44* | *1* | *0.99(0.97-1.01)* | *0.197* | *0.00699* |
| rs7072776 | 10 | 22032942 | G/A | 0.28 | 1.09(1.05-1.14) | 1.79x10$^{-06}$ | 0.29 | 1 | 1.07(1.05-1.09) | 7.66x10$^{-10}$ | 1.29x10$^{-14}$ |
| rs11814448 | 10 | 22315843 | A/C | 0.02 | 1.35(1.17-1.56) | 3.83x10$^{-05}$ | 0.02 | 1 | 1.27(1.19-1.36) | 2.73x10$^{-13}$ | 6.47x10$^{-17}$ |
| rs10995190 | 10 | 64278682 | G/A | 0.15 | 0.86(0.82-0.91) | 1.30x10$^{-09}$ | 0.16 | 1 | 0.86(0.83-0.88) | 1.60x10$^{-29}$ | 1.50x10$^{-37}$ |
| rs704010 | 10 | 80841148 | C/T | 0.39 | 1.11(1.08-1.15) | 6.32x10$^{-10}$ | 0.38 | 1 | 1.08(1.06-1.1) | 2.94x10$^{-15}$ | 3.15x10$^{-23}$ |
| rs7904519 | 10 | 114773927 | A/G | 0.45 | 1.09(1.05-1.12) | 1.20x10$^{-06}$ | 0.46 | 1 | 1.05(1.03-1.07) | 4.74x10$^{-08}$ | 9.21x10$^{-13}$ |
| rs11199914 | 10 | 123093901 | C/T | 0.32 | 0.94(0.91-0.97) | 0.000822 | 0.32 | 1 | 0.95(0.93-0.97) | 2.25x10$^{-06}$ | 8.20x10$^{-09}$ |
| rs2981579 | 10 | 123337335 | G/A | 0.42 | 1.25(1.21-1.29) | 2.21x10$^{-37}$ | 0.4 | 1 | 1.27(1.24-1.29) | 1.29x10$^{-128}$ | 5.89x10$^{-164}$ |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs3817198 | 11 | 1909006 | T/C | 0.32 | 1.07(1.03-1.11) | 0.000454 | 0.31 | 1 | 1.07(1.05-1.09) | $1.09x10^{-10}$ | $2.09x10^{-13}$ |
| rs3903072 | 11 | 65583066 | G/T | 0.47 | 0.93(0.9-0.97) | $5.50x10^{-05}$ | 0.47 | 1 | 0.95(0.93-0.97) | $3.02x10^{-07}$ | $1.14x10^{-10}$ |
| rs78540526 | 11 | 69331418 | C/T | 0.08 | 1.42(1.33-1.51) | $2.30x10^{-26}$ | 0.08 | 0.99 | 1.34(1.29-1.38) | $1.65x10^{-62}$ | $1.65x10^{-86}$ |
| rs554219 | 11 | 69331642 | C/G | 0.13 | 1.28(1.22-1.34) | $2.66x10^{-23}$ | 0.12 | 1 | 1.26(1.23-1.3) | $6.25x10^{-60}$ | $2.03x10^{-81}$ |
| rs75915166 | 11 | 69379161 | C/A | 0.06 | 1.36(1.27-1.47) | $3.04x10^{-16}$ | 0.06 | 1 | 1.31(1.26-1.36) | $2.40x10^{-43}$ | $1.00x10^{-57}$ |
| rs11820646 | 11 | 129461171 | C/T | 0.41 | 0.94(0.9-0.97) | 0.00013 | 0.41 | 1 | 0.95(0.93-0.97) | $1.72x10^{-07}$ | $1.22x10^{-10}$ |
| *rs12422552** | *12* | *14413931* | *G/C* | *0.26* | *1.08(1.04-1.12)* | *0.000104* | *0.26* | *1* | *1.04(1.02-1.07)* | *$9.42x10^{-05}$* | *$1.14x10^{-07}$* |
| rs10771399 | 12 | 28155080 | A/G | 0.11 | 0.8(0.75-0.84) | $2.22x10^{-14}$ | 0.12 | 1 | 0.86(0.83-0.89) | $2.05x10^{-22}$ | $4.76x10^{-34}$ |
| rs17356907 | 12 | 96027759 | A/G | 0.3 | 0.92(0.89-0.96) | $2.34x10^{-05}$ | 0.3 | 1 | 0.91(0.9-0.93) | $5.62x10^{-17}$ | $7.02x10^{-21}$ |
| rs1292011 | 12 | 115836522 | A/G | 0.42 | 0.92(0.89-0.95) | $2.62x10^{-06}$ | 0.42 | 1 | 0.92(0.9-0.94) | $1.22x10^{-16}$ | $1.72x10^{-21}$ |
| *rs11571833** | *13* | *32972626* | *A/T* | *0.01* | *1.22(0.96-1.54)* | *0.0999* | *0.01* | *1* | *1.27(1.15-1.4)* | *$2.16x10^{-06}$* | *$5.57x10^{-07}$* |
| rs2236007 | 14 | 37132769 | G/A | 0.2 | 0.93(0.89-0.97) | 0.000452 | 0.21 | 1 | 0.93(0.91-0.95) | $4.74x10^{-10}$ | $8.84x10^{-13}$ |
| rs2588809 | 14 | 68660428 | C/T | 0.15 | 1.02(0.97-1.07) | 0.395 | 0.16 | 1 | 1.08(1.05-1.11) | $3.72x10^{-09}$ | $2.28x10^{-08}$ |
| rs999737 | 14 | 69034682 | C/T | 0.23 | 0.88(0.84-0.91) | $1.06x10^{-10}$ | 0.23 | 1 | 0.92(0.9-0.94) | $4.10x10^{-13}$ | $1.98x10^{-21}$ |
| rs941764 | 14 | 91841069 | A/G | 0.33 | 1.04(1-1.08) | 0.0482 | 0.34 | 1 | 1.07(1.05-1.09) | $2.37x10^{-10}$ | $6.22x10^{-11}$ |
| rs3803662 | 16 | 52586341 | G/A | 0.28 | 1.25(1.2-1.29) | $1.08x10^{-32}$ | 0.26 | 1 | 1.24(1.21-1.26) | $2.71x10^{-86}$ | $4.15x10^{-117}$ |
| rs17817449 | 16 | 53813367 | T/G | 0.4 | 0.95(0.92-0.99) | 0.00517 | 0.4 | 1 | 0.93(0.91-0.95) | $6.90x10^{-13}$ | $2.47x10^{-14}$ |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs11075995 | 16 | 53855291 | T/A | 0.23 | 1.08(1.04-1.12) | 0.000218 | 0.24 | 1 | 1.04(1.02-1.06) | 0.000496 | $1.36x10^{-06}$ |
| rs13329835 | 16 | 80650805 | A/G | 0.22 | 1.11(1.06-1.15) | $4.41x10^{-07}$ | 0.22 | 1 | 1.08(1.06-1.11) | $6.08x10^{-12}$ | $2.36x10^{-17}$ |
| rs6504950 | 17 | 53056471 | G/A | 0.28 | 0.93(0.9-0.96) | 0.00012 | 0.28 | 1 | 0.94(0.92-0.96) | $8.15x10^{-09}$ | $4.76x10^{-12}$ |
| rs527616 | 18 | 24337424 | G/C | 0.37 | 0.9(0.86-0.93) | $4.27x10^{-08}$ | 0.38 | 1 | 0.95(0.93-0.97) | $1.47x10^{-07}$ | $7.50x10^{-13}$ |
| rs1436904 | 18 | 24570667 | T/G | 0.41 | 0.95(0.92-0.98) | 0.00174 | 0.4 | 1 | 0.96(0.94-0.97) | $4.73x10^{-06}$ | $3.23x10^{-08}$ |
| rs8170 | 19 | 17389704 | G/A | 0.19 | 1.09(1.05-1.14) | $7.75x10^{-05}$ | 0.19 | 1 | 1.04(1.02-1.07) | 0.000997 | $1.66x10^{-06}$ |
| rs2363956 | 19 | 17394124 | G/T | 0.49 | 1.08(1.04-1.12) | $9.58x10^{-06}$ | 0.49 | 1 | 1.03(1.01-1.05) | 0.00368 | $2.49x10^{-06}$ |
| rs4808801 | 19 | 18571141 | A/G | 0.34 | 0.95(0.92-0.99) | 0.00764 | 0.35 | 1 | 0.93(0.91-0.94) | $5.89x10^{-14}$ | $4.12x10^{-15}$ |
| rs3760982 | 19 | 44286513 | G/A | 0.47 | 1.04(1.01-1.07) | 0.0218 | 0.46 | 1 | 1.05(1.03-1.07) | $9.64x10^{-08}$ | $8.00x10^{-09}$ |
| rs2823093 | 21 | 16520832 | G/A | 0.26 | 0.95(0.92-0.99) | 0.0154 | 0.27 | 1 | 0.93(0.91-0.95) | $2.39x10^{-12}$ | $3.18x10^{-13}$ |
| rs17879961[10] | 22 | 29121087 | A/G | 0.03 | 0.93(0.7-1.23) | 0.593 | 0.0049 | 1 | 1.37(1.21-1.55) | $7.85x10^{-07}$ | $1.67x10^{-5}$ |
| rs132390 | 22 | 29621477 | T/C | 0.03 | 1.2(1.07-1.34) | 0.00163 | 0.04 | 1 | 1.14(1.08-1.2) | $3.79x10^{-07}$ | $3.22x10^{-09}$ |
| rs6001930 | 22 | 40876234 | T/C | 0.1 | 1.17(1.1-1.23) | $4.00x10^{-08}$ | 0.11 | 1 | 1.12(1.09-1.16) | $3.53x10^{-14}$ | $1.71x10^{-20}$ |

[1]SNPs marked in bold and asterisked do not reach $P<5x10^{-8}$ for overall, ER-positive or ER-negative breast cancer.

[2]Chromosome.

[3]Build 37 position.

[4]Reference/effect allele (forward strand).

[5]Mean frequency of the effect allele.

[6]Per-allele OR for the effect allele.

[7]1 degree of freedom trend test.

[8]Mean imputation $r^2$ from IMPUTE2 ($r^2$=1 for genotyped SNPs).

[9]Combined *P*-value based on meta-analysis of the GWAS and iCOGS results.

[10]rs17879961 was not included in the main analysis as MAF <0.005 in iCOGS.

∗ Variants that do not reach $P<5x10^{-8}$ in overall, ER-negative or ER-positive disease

**Supplementary Table 3b:** Association results for ER-positive breast cancer.

| SNP[1] | Chr[2] | Position[3] | Alleles[4] | MAF GWAS[5] | OR GWAS (95%CI)[6] | GWAS *P*[7] | MAF iCOGS[5] | $r^2$ iCOGS[8] | OR iCOGS (95% CI)[6] | iCOGS *P*[7] | Combined *P*[9] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs616488 | 1 | 10566215 | A/G | 0.32 | 0.98(0.9-1.07) | 0.661 | 0.33 | 1 | 0.96(0.94-0.98) | 0.00106 | 0.00107 |
| rs11552449 | 1 | 114448389 | C/T | 0.17 | 1.12(1-1.24) | 0.0423 | 0.16 | 1 | 1.08(1.05-1.11) | $3.06\times10^{-07}$ | $4.30\times10^{-08}$ |
| rs11249433 | 1 | 121280613 | A/G | 0.39 | 1.11(1.03-1.21) | 0.00988 | 0.4 | 1 | 1.12(1.09-1.14) | $5.37\times10^{-22}$ | $1.87\times10^{-23}$ |
| rs6678914 | 1 | 202187176 | G/A | 0.43 | 1.01(0.93-1.1) | 0.754 | 0.41 | 1 | 1.01(0.99-1.04) | 0.308 | 0.286 |
| rs4245739 | 1 | 204518842 | A/C | 0.24 | 0.94(0.85-1.03) | 0.195 | 0.26 | 1 | 1(0.98-1.03) | 0.878 | 0.847 |
| rs12710696 | 2 | 19320803 | C/T | 0.35 | 1.06(0.98-1.15) | 0.159 | 0.36 | 1 | 1.01(0.98-1.03) | 0.531 | 0.325 |
| rs4849887 | 2 | 121245122 | C/T | 0.09 | 0.89(0.77-1.02) | 0.102 | 0.1 | 1 | 0.91(0.88-0.95) | $1.73\times10^{-06}$ | $4.51\times10^{-07}$ |
| rs2016394 | 2 | 172972971 | G/A | 0.48 | 0.94(0.86-1.01) | 0.1 | 0.48 | 1 | 0.94(0.92-0.96) | $1.98\times10^{-08}$ | $4.93\times10^{-09}$ |
| *rs1550623** | *2* | *174212894* | A/G | *0.16* | *0.88(0.79-0.99)* | *0.0289* | *0.16* | *1* | *0.95(0.92-0.98)* | *0.000877* | *0.000148* |
| *rs1045485** | *2* | *202149589* | G/C | *0.13* | *0.92(0.82-1.04)* | *0.205* | *0.13* | *1* | *0.98(0.94-1.01)* | *0.181* | *0.103* |
| rs13387042 | 2 | 217905832 | A/G | 0.49 | 0.82(0.75-0.88) | $5.46\times10^{-07}$ | 0.49 | 1 | 0.86(0.84-0.88) | $2.26\times10^{-37}$ | $1.90\times10^{-42}$ |
| rs16857609 | 2 | 218296508 | C/T | 0.28 | 1.02(0.93-1.11) | 0.693 | 0.26 | 1 | 1.09(1.06-1.11) | $2.35\times10^{-10}$ | $5.46\times10^{-10}$ |
| rs6762644 | 3 | 4742276 | A/G | 0.39 | 1.13(1.05-1.23) | 0.00226 | 0.4 | 1 | 1.07(1.05-1.09) | $8.05\times10^{-09}$ | $1.74\times10^{-10}$ |
| rs4973768 | 3 | 27416013 | C/T | 0.46 | 1.15(1.06-1.25) | 0.000491 | 0.47 | 1 | 1.1(1.08-1.13) | $1.05\times10^{-17}$ | $3.91\times10^{-20}$ |
| rs12493607 | 3 | 30682939 | G/C | 0.35 | 1.05(0.96-1.14) | 0.261 | 0.34 | 1 | 1.07(1.04-1.09) | $5.67\times10^{-08}$ | $3.18\times10^{-08}$ |
| rs1053338 | 3 | 63967900 | A/G | 0.12 | 1.09(0.96-1.23) | 0.18 | 0.13 | 1 | 1.04(1.08-1.11) | $2.86\times10^{-06}$ | $1.11\times10^{-06}$ |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs9790517 | 4 | 106084778 | C/T | 0.23 | 1.08(0.98-1.18) | 0.139 | 0.22 | 1 | 1.06(1.03-1.09) | $1.54x10^{-05}$ | $5.07x10^{-06}$ |
| rs6828523 | 4 | 175846426 | C/A | 0.12 | 0.86(0.76-0.98) | 0.0191 | 0.12 | 1 | 0.87(0.84-0.9) | $1.54x10^{-14}$ | $9.56x10^{-16}$ |
| rs10069690 | 5 | 1279790 | C/T | 0.27 | 1(0.9-1.11) | 0.946 | 0.26 | 1 | 1.04(1.01-1.06) | 0.00778 | 0.0101 |
| *rs7726159** | *5* | *1282319* | C/A | *0.35* | *0.98(0.89-1.08)* | *0.709* | *0.34* | *1* | *1.03(1.01-1.06)* | *0.00676* | *0.0112* |
| rs2736108 | 5 | 1297488 | C/T | 0.26 | 0.98(0.88-1.09) | 0.724 | 0.29 | 1 | 0.96(0.94-0.99) | 0.00239 | 0.00239 |
| rs10941679 | 5 | 44706498 | A/G | 0.25 | 1.19(1.09-1.31) | 0.000236 | 0.25 | 1 | 1.15(1.12-1.18) | $2.84x10^{-28}$ | $4.00x10^{-31}$ |
| rs889312 | 5 | 56031884 | A/C | 0.28 | 1.07(0.98-1.17) | 0.124 | 0.28 | 1 | 1.14(1.12-1.17) | $1.39x10^{-26}$ | $1.07x10^{-26}$ |
| rs10472076 | 5 | 58184061 | T/C | 0.37 | 1.1(1.01-1.19) | 0.027 | 0.38 | 1 | 1.04(1.01-1.06) | 0.00191 | 0.000339 |
| rs1353747 | 5 | 58337481 | T/G | 0.09 | 0.95(0.82-1.09) | 0.442 | 0.1 | 1 | 0.93(0.89-0.97) | 0.00025 | 0.000187 |
| rs1432679 | 5 | 158244083 | T/C | 0.44 | 1.07(0.99-1.16) | 0.102 | 0.43 | 1 | 1.07(1.04-1.09) | $8.23x10^{-09}$ | $2.08x10^{-09}$ |
| *rs11242675** | *6* | *1318878* | T/C | *0.4* | *0.97(0.89-1.05)* | *0.455* | *0.38* | *1* | *0.96(0.94-0.98)* | *0.000754* | *0.000572* |
| rs204247 | 6 | 13722523 | A/G | 0.44 | 1.03(0.95-1.12) | 0.501 | 0.44 | 1 | 1.07(1.04-1.09) | $3.55x10^{-08}$ | $3.98x10^{-08}$ |
| rs17529111 | 6 | 82128386 | T/C | 0.23 | 1.13(1.03-1.24) | 0.0124 | 0.22 | 1 | 1.06(1.03-1.09) | $3.61x10^{-05}$ | $3.22x10^{-06}$ |
| rs12662670 | 6 | 151918856 | T/G | 0.07 | 1.12(0.96-1.32) | 0.157 | 0.07 | 1 | 1.13(1.08-1.18) | $2.05x10^{-08}$ | $7.33x10^{-09}$ |
| rs2046210 | 6 | 151948366 | G/A | 0.31 | 1.1(1.01-1.19) | 0.0342 | 0.34 | 1 | 1.06(1.03-1.08) | $1.00x10^{-05}$ | $1.42x10^{-06}$ |
| *rs6964587** | *7* | *91630620* | *G/T* | *0.39* | *1.03(0.94-1.11)* | *0.55* | *0.39* | *1* | *1.06(1.04-1.08)* | *$5.78x10^{-07}$* | *$6.46x10^{-07}$* |
| rs720475 | 7 | 144074929 | G/A | 0.25 | 0.99(0.9-1.09) | 0.852 | 0.25 | 1 | 0.93(0.91-0.96) | $1.03x10^{-07}$ | $2.34x10^{-07}$ |
| rs9693444 | 8 | 29509616 | C/A | 0.33 | 1.05(0.96-1.14) | 0.264 | 0.32 | 1 | 1.07(1.05-1.1) | $1.28x10^{-08}$ | $7.49x10^{-09}$ |
| rs6472903 | 8 | 76230301 | T/G | 0.18 | 0.89(0.8-0.99) | 0.0254 | 0.18 | 1 | 0.91(0.88-0.94) | $1.14x10^{-09}$ | $1.00x10^{-10}$ |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| rs2943559 | 8 | 76417937 | A/G | 0.07 | 1.06(0.9-1.24) | 0.517 | 0.07 | 1 | 1.13(1.09-1.18) | $4.64x10^{-09}$ | $5.38x10^{-09}$ |
| rs13281615 | 8 | 128355618 | A/G | 0.4 | 1.18(1.09-1.28) | 7.04E-05 | 0.4 | 1 | 1.11(1.08-1.13) | $5.45x10^{-18}$ | $5.73x10^{-21}$ |
| rs11780156 | 8 | 129194641 | C/T | 0.15 | 1.15(1.03-1.29) | 0.012 | 0.16 | 1 | 1.07(1.04-1.11) | $5.31x10^{-06}$ | $4.39x10^{-07}$ |
| rs1011970 | 9 | 22062134 | G/T | 0.18 | 1.08(0.97-1.2) | 0.151 | 0.17 | 1 | 1.04(1.01-1.08) | 0.00438 | 0.00173 |
| rs10759243 | 9 | 110306115 | C/A | 0.28 | 1.02(0.93-1.11) | 0.707 | 0.29 | 1 | 1.08(1.05-1.11) | $1.48x10^{-09}$ | $2.91x10^{-09}$ |
| rs865686 | 9 | 110888478 | T/G | 0.38 | 0.86(0.79-0.94) | 0.000502 | 0.38 | 1 | 0.87(0.85-0.89) | $2.14x10^{-30}$ | $4.93x10^{-33}$ |
| *rs2380205** | *10* | *5886734* | C/T | *0.45* | *0.91(0.84-0.99)* | *0.0273* | *0.44* | *1* | *0.98(0.96-1)* | *0.062* | *0.0167* |
| rs7072776 | 10 | 22032942 | G/A | 0.26 | 1.14(1.04-1.25) | 0.00436 | 0.28 | 1 | 1.09(1.06-1.12) | $1.17x10^{-11}$ | $2.96x10^{-13}$ |
| rs11814448 | 10 | 22315843 | A/C | 0.02 | 1.11(0.8-1.55) | 0.53 | 0.02 | 1 | 1.27(1.18-1.37) | 6.44E-10 | $7.08x10^{-10}$ |
| rs10995190 | 10 | 64278682 | G/A | 0.17 | 0.84(0.75-0.93) | 0.00153 | 0.16 | 1 | 0.85(0.83-0.88) | $9.68x10^{-23}$ | $6.37x10^{-25}$ |
| rs704010 | 10 | 80841148 | C/T | 0.37 | 1.07(0.98-1.16) | 0.132 | 0.38 | 1 | 1.1(1.07-1.12) | $2.09x10^{-15}$ | $8.34x10^{-16}$ |
| rs7904519 | 10 | 114773927 | A/G | 0.45 | 1.11(1.02-1.2) | 0.0116 | 0.46 | 1 | 1.04(1.02-1.07) | 0.000168 | $1.70x10^{-05}$ |
| rs11199914 | 10 | 123093901 | C/T | 0.34 | 0.93(0.85-1.01) | 0.1 | 0.32 | 1 | 0.93(0.91-0.96) | $5.50x10^{-08}$ | $1.38x10^{-08}$ |
| rs2981579 | 10 | 123337335 | G/A | 0.41 | 1.37(1.26-1.49) | $5.12x10^{-14}$ | 0.4 | 1 | 1.33(1.3-1.36) | $9.36x10^{-133}$ | $5.79x10^{-145}$ |
| rs3817198 | 11 | 1909006 | T/C | 0.3 | 1.01(0.92-1.1) | 0.888 | 0.31 | 1 | 1.09(1.06-1.11) | $1.55x10^{-11}$ | $6.16x10^{-11}$ |
| rs3903072 | 11 | 65583066 | G/T | 0.5 | 0.9(0.83-0.97) | 0.00878 | 0.47 | 1 | 0.95(0.92-0.97) | $1.11x10^{-06}$ | $6.87x10^{-08}$ |
| rs78540526 | 11 | 69331418 | C/T | 0.08 | 1.37(1.19-1.59) | 1.87E-05 | 0.08 | 0.99 | 1.41(1.35-1.46) | $2.31x10^{-66}$ | $2.50x10^{-70}$ |
| rs554219 | 11 | 69331642 | C/G | 0.13 | 1.35(1.2-1.51) | 6.55E-07 | 0.12 | 1 | 1.32(1.28-1.37) | $9.07x10^{-65}$ | $3.82x10^{-70}$ |
| rs75915166 | 11 | 69379161 | C/A | 0.06 | 1.23(1.03-1.46) | 0.0204 | 0.06 | 1 | 1.38(1.32-1.44) | $9.52x10^{-46}$ | $1.48x10^{-46}$ |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| rs11820646 | 11 | 129461171 | C/T | 0.43 | 0.92(0.85-1) | 0.0514 | 0.41 | 1 | 0.95(0.93-0.97) | $2.68x10^{-06}$ | $4.48x10^{-07}$ |
| *rs12422552** | *12* | *14413931* | G/C | *0.25* | *1.14(1.04-1.25)* | *0.00592* | *0.26* | *1* | *1.04(1.01-1.07)* | *0.00204* | *0.000217* |
| rs10771399 | 12 | 28155080 | A/G | 0.11 | 0.82(0.72-0.94) | 0.00389 | 0.12 | 1 | 0.88(0.85-0.91) | $5.77x10^{-13}$ | $1.23x10^{-14}$ |
| rs17356907 | 12 | 96027759 | A/G | 0.31 | 0.89(0.82-0.98) | 0.0157 | 0.3 | 1 | 0.91(0.89-0.93) | $1.47x10^{-14}$ | $7.99x10^{-16}$ |
| rs1292011 | 12 | 115836522 | A/G | 0.41 | 0.88(0.82-0.96) | 0.00346 | 0.42 | 1 | 0.91(0.89-0.93) | $8.75x10^{-17}$ | $1.36x10^{-18}$ |
| *rs11571833** | *13* | *32972626* | A/T | *0.01* | *1.64(1.03-2.62)* | *0.0374* | *0.01* | *1* | *1.26(1.12-1.41)* | *0.00013* | *$2.47x10^{-05}$* |
| rs2236007 | 14 | 37132769 | G/A | 0.2 | 0.87(0.78-0.96) | 0.00649 | 0.21 | 1 | 0.91(0.89-0.94) | $1.55x10^{-10}$ | $5.48x10^{-12}$ |
| rs2588809 | 14 | 68660428 | C/T | 0.16 | 1.04(0.93-1.16) | 0.467 | 0.16 | 1 | 1.09(1.06-1.13) | $4.89x10^{-09}$ | $5.39x10^{-09}$ |
| rs999737 | 14 | 69034682 | C/T | 0.23 | 0.86(0.78-0.94) | 0.00153 | 0.23 | 1 | 0.91(0.89-0.94) | $5.00x10^{-11}$ | $6.90x10^{-13}$ |
| rs941764 | 14 | 91841069 | A/G | 0.34 | 1.07(0.99-1.17) | 0.104 | 0.34 | 1 | 1.07(1.05-1.1) | $3.66x10^{-09}$ | $9.41x10^{-10}$ |
| rs3803662 | 16 | 52586341 | G/A | 0.28 | 1.28(1.17-1.39) | 3.43E-08 | 0.26 | 1 | 1.26(1.23-1.29) | $4.02x10^{-73}$ | $9.98x10^{-80}$ |
| rs17817449 | 16 | 53813367 | T/G | 0.4 | 0.98(0.9-1.06) | 0.552 | 0.4 | 1 | 0.93(0.91-0.96) | $5.77x10^{-09}$ | $8.03x10^{-09}$ |
| rs11075995 | 16 | 53855291 | T/A | 0.25 | 1.06(0.96-1.16) | 0.235 | 0.24 | 1 | 1.03(1-1.05) | 0.0473 | 0.0258 |
| rs13329835 | 16 | 80650805 | A/G | 0.23 | 1.09(0.99-1.2) | 0.0716 | 0.22 | 1 | 1.09(1.06-1.12) | $1.64x10^{-10}$ | $3.12x10^{-11}$ |
| rs6504950 | 17 | 53056471 | G/A | 0.27 | 0.95(0.87-1.04) | 0.279 | 0.28 | 1 | 0.93(0.91-0.95) | $2.94x10^{-08}$ | $1.79x10^{-08}$ |
| rs527616 | 18 | 24337424 | G/C | 0.41 | 0.9(0.82-0.98) | 0.0118 | 0.38 | 1 | 0.95(0.93-0.98) | $4.49x10^{-05}$ | $4.28x10^{-06}$ |
| rs1436904 | 18 | 24570667 | T/G | 0.39 | 0.94(0.87-1.03) | 0.177 | 0.4 | 1 | 0.94(0.92-0.96) | $1.44x10^{-07}$ | $5.65x10^{-08}$ |
| rs8170 | 19 | 17389704 | G/A | 0.2 | 0.95(0.85-1.05) | 0.285 | 0.19 | 1 | 1.01(0.98-1.04) | 0.597 | 0.825 |
| rs2363956 | 19 | 17394124 | G/T | 0.46 | 0.97(0.89-1.05) | 0.396 | 0.49 | 1 | 1(0.98-1.02) | 0.946 | 0.767 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs4808801 | 19 | 18571141 | A/G | 0.35 | 0.95(0.87-1.03) | 0.238 | 0.35 | 1 | 0.93(0.91-0.95) | $3.82\times10^{-10}$ | $2.18\times10^{-10}$ |
| rs3760982 | 19 | 44286513 | G/A | 0.45 | 1.07(0.99-1.16) | 0.102 | 0.46 | 1 | 1.06(1.04-1.08) | $5.08\times10^{-07}$ | $1.30\times10^{-07}$ |
| rs2823093 | 21 | 16520832 | G/A | 0.27 | 0.97(0.87-1.07) | 0.546 | 0.27 | 1 | 0.91(0.89-0.94) | $3.18\times10^{-12}$ | $4.81\times10^{-12}$ |
| rs17879961 | 22 | 29121087 | A/G | 0.04 | 0.89(0.57-1.36) | 0.582 | 0.0049 | 1 | 1.51(1.31-1.73) | $3.49\times10^{-09}$ | $2.81\times10^{-08}$ |
| rs132390 | 22 | 29621477 | T/C | 0.04 | 1.17(0.93-1.48) | 0.177 | 0.04 | 1 | 1.14(1.08-1.21) | $8.44\times10^{-06}$ | $3.35\times10^{-06}$ |
| rs6001930 | 22 | 40876234 | T/C | 0.12 | 1.08(0.95-1.22) | 0.24 | 0.11 | 1 | 1.12(1.08-1.16) | $2.81\times10^{-10}$ | $1.64\times10^{-10}$ |

[1]SNPs marked in bold and asterisked do not reach $P<5\times10^{-8}$ for overall, ER-positive or ER-negative breast cancer.

[2]Chromosome.

[3]Build 37 position.

[4]Reference/effect allele, based on the overall frequency in controls in iCOGS (forward strand).

[5]Mean frequency of the effect allele.

[6]Per-allele OR for the effect allele.

[7]1 degree of freedom trend test.

[8]Mean imputation $r^2$ from IMPUTE2 ($r^2=1$ for genotyped SNPs).

[9]Combined *P*-value based on meta-analysis of the GWAS and iCOGS results.

[10]rs17879961 was not included in the main analysis as MAF <0.005 in iCOGS.

∗ Variants that do not reach $P<5\times10^{-8}$ in overall, ER-negative or ER-positive disease

**Supplementary Table 3c.** Association results for ER-negative breast cancer.

| SNP[1] | Chr[2] | Position[3] | Alleles[4] | MAF GWAS[5] | OR GWAS (95%CI)[6] | GWAS *P*[7] | MAF iCOGS[5] | $r^2$ iCOGS[8] | OR iCOGS (95%CI)[6] | iCOGS *P*[7] | Combine *P*[9] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs616488 | 1 | 10566215 | A/G | 0.33 | 0.92(0.87-0.97) | 0.0033 | 0.33 | 1 | 0.91(0.87-0.95) | 3.91E-06 | $2.99x10^{-08}$ |
| rs11552449 | 1 | 114448389 | C/T | 0.17 | 1.09(1.02-1.17) | 0.0159 | 0.16 | 1 | 1.04(0.99-1.1) | 0.0833 | 0.00689 |
| rs11249433 | 1 | 121280613 | A/G | 0.42 | 1.06(1-1.13) | 0.066 | 0.4 | 1 | 1(0.96-1.04) | 0.938 | 0.334 |
| rs6678914 | 1 | 202187176 | G/A | 0.41 | 0.88(0.83-0.93) | $2.32x10^{-06}$ | 0.41 | 1 | 0.92(0.88-0.96) | 1.69E-05 | $3.83x10^{-10}$ |
| rs4245739 | 1 | 204518842 | A/C | 0.28 | 1.12(1.05-1.18) | 0.000218 | 0.26 | 1 | 1.15(1.11-1.2) | 1.75E-11 | $1.23x10^{-14}$ |
| rs12710696 | 2 | 19320803 | C/T | 0.37 | 1.07(1.02-1.13) | 0.00955 | 0.36 | 1 | 1.1(1.06-1.14) | 1.24E-06 | $3.95x10^{-08}$ |
| rs4849887 | 2 | 121245122 | C/T | 0.1 | 0.96(0.88-1.05) | 0.345 | 0.1 | 1 | 0.9(0.85-0.96) | 0.00223 | 0.00233 |
| rs2016394 | 2 | 172972971 | G/A | 0.47 | 1.07(1.01-1.12) | 0.013 | 0.48 | 1 | 1(0.96-1.03) | 0.817 | 0.161 |
| *rs1550623** | *2* | *174212894* | *A/G* | *0.16* | *0.98(0.91-1.05)* | *0.572* | *0.16* | *1* | *0.95(0.91-1.01)* | *0.0784* | *0.0651* |
| *rs1045485** | *2* | *202149589* | *G/C* | *0.13* | *0.9(0.83-0.97)* | *0.00887* | *0.13* | *1* | *0.98(0.92-1.03)* | *0.43* | *0.0198* |
| rs13387042 | 2 | 217905832 | A/G | 0.48 | 0.94(0.9-0.99) | 0.0263 | 0.49 | 1 | 0.96(0.93-1) | 0.0345 | 0.00158 |
| rs16857609 | 2 | 218296508 | C/T | 0.26 | 1.06(1-1.13) | 0.0466 | 0.26 | 1 | 1.09(1.04-1.13) | 0.000101 | $3.06x10^{-05}$ |
| rs6762644 | 3 | 4742276 | A/G | 0.39 | 0.98(0.93-1.04) | 0.502 | 0.4 | 1 | 1.02(0.98-1.06) | 0.276 | 0.719 |
| rs4973768 | 3 | 27416013 | C/T | 0.48 | 1.03(0.97-1.08) | 0.326 | 0.47 | 1 | 1.05(1.01-1.09) | 0.00897 | 0.00662 |
| rs12493607 | 3 | 30682939 | G/C | 0.35 | 0.99(0.94-1.05) | 0.823 | 0.34 | 1 | 1.02(0.98-1.06) | 0.373 | 0.527 |
| rs1053338 | 3 | 63967900 | A/G | 0.12 | 1.02(0.94-1.10) | 0.63 | 0.13 | 1 | 1.06(1.00-1.12) | 0.04 | 0.05 |
| rs9790517 | 4 | 106084778 | C/T | 0.23 | 1.1(1.03-1.17) | 0.00306 | 0.22 | 1 | 1.03(0.98-1.07) | 0.275 | 0.00896 |
| rs6828523 | 4 | 175846426 | C/A | 0.12 | 0.94(0.86-1.02) | 0.136 | 0.12 | 1 | 1.02(0.96-1.08) | 0.484 | 0.772 |
| rs10069690 | 5 | 1279790 | C/T | 0.29 | 1.07(0.95-1.21) | 0.261 | 0.26 | 1 | 1.16(1.12-1.21) | $3.97x10^{-13}$ | $5.84x10^{-13}$ |
| *rs7726159** | *5* | *1282319* | C/A | *0.35* | *1.07(0.98-1.16)* | *0.129* | *0.34* | *1* | *1.09(1.05-1.14)* | *$9.75x10^{-06}$* | *$2.19x10^{-06}$* |
| rs2736108 | 5 | 1297488 | C/T | 0.26 | 0.93(0.84-1.03) | 0.168 | 0.29 | 1 | 0.89(0.85-0.93) | $5.13x10^{-08}$ | $1.41x10^{-08}$ |
| rs10941679 | 5 | 44706498 | A/G | 0.24 | 1.07(0.98-1.16) | 0.129 | 0.25 | 1 | 1.03(0.99-1.08) | 0.147 | 0.0352 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs889312 | 5 | 56031884 | A/C | 0.28 | 1.07(1.01-1.14) | 0.0142 | 0.28 | 1 | 1.06(1.02-1.1) | 0.00663 | 0.000239 |
| rs10472076 | 5 | 58184061 | T/C | 0.36 | 1.04(0.99-1.1) | 0.134 | 0.38 | 1 | 1.06(1.02-1.1) | 0.00464 | 0.0023 |
| rs1353747 | 5 | 58337481 | T/G | 0.09 | 0.97(0.89-1.06) | 0.512 | 0.1 | 1 | 0.92(0.86-0.98) | 0.00835 | 0.0098 |
| rs1432679 | 5 | 158244083 | T/C | 0.43 | 1.06(1-1.11) | 0.039 | 0.43 | 1 | 1.08(1.04-1.13) | $2.39x10^{-05}$ | $2.83x10^{-06}$ |
| *rs11242675** | *6* | *1318878* | *T/C* | *0.37* | *0.94(0.89-0.99)* | *0.015* | *0.38* | *1* | *0.96(0.92-0.99)* | *0.0217* | *0.00069* |
| rs204247 | 6 | 13722523 | A/G | 0.44 | 1.08(1.03-1.14) | 0.00307 | 0.44 | 1 | 1.01(0.97-1.04) | 0.739 | 0.0489 |
| rs17529111 | 6 | 82128386 | T/C | 0.22 | 1.17(1.08-1.26) | 0.000167 | 0.22 | 1 | 1.05(1-1.09) | 0.0467 | 0.000356 |
| rs12662670 | 6 | 151918856 | T/G | 0.08 | 1.25(1.13-1.37) | $7.53x10^{-06}$ | 0.07 | 1 | 1.24(1.16-1.32) | $3.00x10^{-10}$ | $8.90x10^{-15}$ |
| rs2046210 | 6 | 151948366 | G/A | 0.35 | 1.15(1.09-1.22) | $2.26x10^{-07}$ | 0.34 | 1 | 1.16(1.12-1.21) | $8.88x10^{-14}$ | $4.10x10^{-20}$ |
| *rs6964587** | *7* | *91630620* | *G/T* | *0.39* | *1.01(0.96-1.06)* | *0.79* | *0.39* | *1* | *1.04(1-1.08)* | *0.06* | *0.09* |
| rs720475 | 7 | 144074929 | G/A | 0.24 | 1.03(0.96-1.09) | 0.415 | 0.26 | 1 | 0.99(0.95-1.03) | 0.694 | 0.968 |
| rs9693444 | 8 | 29509616 | C/A | 0.32 | 1.02(0.96-1.07) | 0.567 | 0.32 | 1 | 1.09(1.04-1.13) | 4.66E-05 | 0.000342 |
| rs6472903 | 8 | 76230301 | T/G | 0.18 | 0.97(0.9-1.04) | 0.325 | 0.18 | 1 | 0.94(0.89-0.99) | 0.0126 | 0.00892 |
| rs2943559 | 8 | 76417937 | A/G | 0.07 | 1.16(1.05-1.29) | 0.00384 | 0.07 | 1 | 1.07(1-1.15) | 0.0552 | 0.00133 |
| rs13281615 | 8 | 128355618 | A/G | 0.42 | 1.07(1.01-1.12) | 0.0157 | 0.4 | 1 | 1.03(0.99-1.07) | 0.195 | 0.0129 |
| rs11780156 | 8 | 129194641 | C/T | 0.18 | 1.02(0.95-1.09) | 0.586 | 0.16 | 1 | 1.06(1-1.11) | 0.032 | 0.0365 |
| rs1011970 | 9 | 22062134 | G/T | 0.17 | 1.08(1.01-1.15) | 0.0335 | 0.17 | 1 | 1.11(1.06-1.17) | $1.42x10^{-05}$ | $7.36x10^{-07}$ |
| rs10759243 | 9 | 110306115 | C/A | 0.27 | 1.1(1.02-1.18) | 0.0168 | 0.29 | 1 | 1.01(0.97-1.05) | 0.608 | 0.15 |
| rs865686 | 9 | 110888478 | T/G | 0.36 | 0.97(0.92-1.03) | 0.332 | 0.38 | 1 | 0.99(0.95-1.03) | 0.487 | 0.211 |
| *rs2380205** | *10* | *5886734* | *C/T* | *0.44* | *0.98(0.93-1.03)* | *0.492* | *0.44* | *1* | *1.01(0.97-1.05)* | *0.718* | *0.755* |
| rs7072776 | 10 | 22032942 | G/A | 0.28 | 1.04(0.99-1.11) | 0.136 | 0.29 | 1 | 0.94(0.91-0.98) | 0.00709 | 0.216 |
| rs11814448 | 10 | 22315843 | A/C | 0.02 | 1.22(0.92-1.62) | 0.164 | 0.02 | 1 | 1.2(1.06-1.37) | 0.00399 | 0.00143 |
| rs10995190 | 10 | 64278682 | G/A | 0.15 | 0.92(0.85-0.98) | 0.0173 | 0.16 | 1 | 0.87(0.83-0.92) | $3.34x10^{-07}$ | $3.75x10^{-08}$ |
| rs704010 | 10 | 80841148 | C/T | 0.38 | 1.07(1.02-1.13) | 0.0114 | 0.38 | 1 | 1.03(0.99-1.07) | 0.0969 | 0.00388 |
| rs7904519 | 10 | 114773927 | A/G | 0.46 | 1.12(1.06-1.18) | $3.28x10^{-05}$ | 0.46 | 1 | 1.04(1.01-1.08) | 0.021 | $7.54x10^{-06}$ |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs11199914 | 10 | 123093901 | C/T | 0.32 | 0.96(0.91-1.02) | 0.156 | 0.32 | 1 | 1.02(0.98-1.06) | 0.398 | 0.971 |
| rs2981579 | 10 | 123337335 | G/A | 0.42 | 1.02(0.97-1.08) | 0.367 | 0.4 | 1 | 1.02(0.99-1.06) | 0.205 | 0.0906 |
| rs3817198 | 11 | 1909006 | T/C | 0.32 | 1.06(1-1.12) | 0.0406 | 0.31 | 1 | 1.06(1.02-1.11) | 0.0028 | 0.000401 |
| rs3903072 | 11 | 65583066 | G/T | 0.47 | 0.94(0.89-0.99) | 0.015 | 0.47 | 1 | 0.97(0.94-1.01) | 0.173 | 0.00625 |
| rs78540526 | 11 | 69331418 | C/T | 0.08 | 1.1(0.98-1.24) | 0.108 | 0.08 | 0.99 | 1.03(0.96-1.11) | 0.376 | 0.138 |
| rs554219 | 11 | 69331642 | C/G | 0.13 | 1.08(1-1.17) | 0.0483 | 0.12 | 1 | 1.02(0.96-1.08) | 0.486 | 0.1 |
| rs75915166 | 11 | 69379161 | C/A | 0.07 | 1.04(0.91-1.19) | 0.591 | 0.06 | 1 | 1.06(0.98-1.14) | 0.161 | 0.196 |
| rs11820646 | 11 | 129461171 | C/T | 0.4 | 0.93(0.88-0.98) | 0.0092 | 0.41 | 1 | 0.96(0.92-1) | 0.0295 | 0.000967 |
| *rs12422552** | *12* | *14413931* | *G/C* | *0.26* | *1.08(1.01-1.14)* | *0.0161* | *0.26* | *1* | *1.05(1-1.09)* | *0.0338* | *0.0023* |
| rs10771399 | 12 | 28155080 | A/G | 0.1 | 0.8(0.72-0.87) | $1.46x10^{-06}$ | 0.12 | 1 | 0.84(0.79-0.9) | $5.05x10^{-08}$ | $1.64x10^{-13}$ |
| rs17356907 | 12 | 96027759 | A/G | 0.3 | 0.89(0.84-0.94) | $8.10x10^{-05}$ | 0.3 | 1 | 0.95(0.91-0.99) | 0.0101 | $6.25x10^{-06}$ |
| rs1292011 | 12 | 115836522 | A/G | 0.42 | 0.98(0.93-1.03) | 0.493 | 0.42 | 1 | 0.98(0.95-1.02) | 0.416 | 0.286 |
| *rs11571833** | *13* | *32972626* | A/T | *0.01* | *1.35(0.86-2.11)* | *0.19* | *0.01* | *1* | *1.48(1.24-1.77)* | *$1.57x10^{-05}$* | *$1.01x10^{-05}$* |
| rs2236007 | 14 | 37132769 | G/A | 0.21 | 1(0.94-1.07) | 0.938 | 0.21 | 1 | 0.96(0.92-1) | 0.0777 | 0.118 |
| rs2588809 | 14 | 68660428 | C/T | 0.15 | 0.93(0.86-1.01) | 0.0727 | 0.16 | 1 | 1.01(0.96-1.07) | 0.609 | 0.532 |
| rs999737 | 14 | 69034682 | C/T | 0.23 | 0.92(0.86-0.98) | 0.00631 | 0.23 | 1 | 0.94(0.9-0.98) | 0.00728 | 0.00019 |
| rs941764 | 14 | 91841069 | A/G | 0.32 | 0.96(0.89-1.03) | 0.228 | 0.34 | 1 | 1.04(1-1.08) | 0.0448 | 0.316 |
| rs3803662 | 16 | 52586341 | G/A | 0.29 | 1.12(1.06-1.18) | 0.000139 | 0.26 | 1 | 1.15(1.1-1.19) | $6.51x10^{-11}$ | $5.11x10^{-14}$ |
| rs17817449 | 16 | 53813367 | T/G | 0.4 | 0.96(0.91-1.02) | 0.167 | 0.4 | 1 | 0.91(0.87-0.94) | $3.43x10^{-07}$ | $5.59x10^{-07}$ |
| rs11075995 | 16 | 53855291 | T/A | 0.23 | 1.12(1.05-1.19) | 0.000517 | 0.24 | 1 | 1.1(1.05-1.15) | $1.14x10^{-05}$ | $3.30x10^{-08}$ |
| rs13329835 | 16 | 80650805 | A/G | 0.23 | 1.04(0.98-1.1) | 0.242 | 0.22 | 1 | 1.02(0.98-1.07) | 0.4 | 0.161 |
| rs6504950 | 17 | 53056471 | G/A | 0.28 | 0.96(0.91-1.02) | 0.206 | 0.28 | 1 | 0.98(0.94-1.02) | 0.239 | 0.0824 |
| rs527616 | 18 | 24337424 | G/C | 0.38 | 0.94(0.88-1.01) | 0.0723 | 0.38 | 1 | 0.98(0.94-1.02) | 0.331 | 0.064 |
| rs1436904 | 18 | 24570667 | T/G | 0.4 | 0.98(0.93-1.03) | 0.368 | 0.4 | 1 | 1(0.97-1.04) | 0.816 | 0.689 |
| rs8170 | 19 | 17389704 | G/A | 0.19 | 1.17(1.09-1.25) | 7.74E-06 | 0.19 | 1 | 1.14(1.09-1.2) | $1.94x10^{-08}$ | $9.09x10^{-13}$ |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs2363956 | 19 | 17394124 | G/T | 0.49 | 1.13(1.07-1.19) | 4.53E-06 | 0.49 | 1 | 1.13(1.09-1.17) | $1.79x10^{-10}$ | $3.04x10^{-15}$ |
| rs4808801 | 19 | 18571141 | A/G | 0.34 | 0.99(0.94-1.05) | 0.686 | 0.35 | 1 | 0.92(0.88-0.96) | $2.76x10^{-05}$ | 0.000241 |
| rs3760982 | 19 | 44286513 | G/A | 0.47 | 1.03(0.98-1.09) | 0.247 | 0.46 | 1 | 1.04(1-1.08) | 0.0384 | 0.023 |
| rs2823093 | 21 | 16520832 | G/A | 0.26 | 1.02(0.96-1.08) | 0.59 | 0.27 | 1 | 0.97(0.93-1.01) | 0.13 | 0.417 |
| rs17879961[10] | 22 | 29121087 | A/G | 0.03 | 1.07(0.72-1.59) | 0.748 | 0.0049 | 1 | 1.01(0.78-1.31) | 0.927 | 0.8 |
| rs132390 | 22 | 29621477 | T/C | 0.03 | 0.93(0.74-1.18) | 0.562 | 0.04 | 1 | 1.1(1-1.21) | 0.0511 | 0.156 |
| rs6001930 | 22 | 40876234 | T/C | 0.11 | 1.17(1.08-1.28) | 0.000313 | 0.11 | 1 | 1.1(1.04-1.17) | 0.000866 | $3.91x10^{-06}$ |

[1]SNPs marked in bold and asterisked do not reach $P<5x10^{-8}$ for overall, ER-positive or ER-negative breast cancer.

[2]Chromosome.

[3]Build 37 position.

[4]Reference/effect allele, based on the overall frequency in controls in iCOGS (forward strand).

[5]Mean frequency of the effect allele.

[6]Per-allele OR for the effect allele.

[7]1 degree of freedom trend test.

[8]Mean imputation $r^2$ from IMPUTE2 ($r^2=1$ for genotyped SNPs).

[9]Combined *P*-value based on meta-analysis of the GWAS and iCOGS results.

[10]rs17879961 was not included in the main analysis as MAF <0.005 in iCOGS.

∗ Variants that do not reach $P<5x10^{-8}$ in overall, ER-negative or ER-positive disease

**Supplementary Table 4.** Loci associated with breast cancer at $P<5x10^{-8}$ that failed to reach $P<5x10^{-8}$ after reanalysis in which imputation was performed without pre-phasing (see Online Methods).

| variant | Chromosome | Position[1] | Alleles[2] | MAF[3] | Imputation $r^2$ iCOGS | Original p-value | Re-imputation $r^2$ iCOGS | p-value after re-imputation |
|---|---|---|---|---|---|---|---|---|
| rs754536 | 2 | 25176200 | T/C | 0.48 | 0.68 | $4.23x10^{-9}$ | 0.60 | $2.87x10^{-7}$ |
| rs188193695[4] | 8 | 11174465 | C/T | 0.01 | 0.51 | $2.65x10^{-8}$ | 0.23 | 0.15 |
| rs2229510 | 19 | 12903059 | C/A | 0.03 | 0.73 | $7.11x10^{-9}$ | 0.56 | $1.15x10^{-7}$ |

[1] build 37 position

[2] Reference/effect allele, based on the overall frequency in controls in iCOGS (forward strand).

[3] Mean frequency of the effect allele.

[4] this variant after re-imputation failed the imputation threshold for inclusion in the meta-analysis

**Supplementary Table 5**. Validation of 15 risk loci by direct genotyping in ~4,000 individuals from SEARCH.

| Best variant | Chromosome | Position[1] | Highly correlated SNP genotyped on iCOGS | Reasons for selection on iCOGS | Imputation[2] $r^2$ iCOGS | Correlation[3] | Estimate[4] imputed | Estimate[5] genotyped |
|---|---|---|---|---|---|---|---|---|
| rs12405132 | 1 | 145644984 | - | | 0.96 | 0.99 | -0.029 | -0.026 |
| rs12048493 | 1 | 149927034 | rs11205227 | Published GWAS hit for height[9] | - | - | - | - |
| rs72755295 | 1 | 242034263 | rs4149909 | Breast cancer combined GWAS, menopause association, candidate from OCAC | - | - | - | - |
| rs6796502 | 3 | 46866866 | - | | 0.91 | 0.95 | -0.062 | -0.068 |
| rs13162653[6] | 5 | 16187528 | - | | 0.72 | 0.7 | -0.066 | -0.057 |
| rs2012709 | 5 | 32567732 | - | | 0.81 | 0.84 | 0.109 | 0.114 |
| rs7707921 | 5 | 81538046 | - | | 0.88 | 0.94 | -0.135 | -0.135 |
| rs9257408[7] | 6 | 28926220 | - | | 0.92 | - | - | - |
| rs4593472 | 7 | 130667121 | rs4593472 | Breast cancer combined GWAS | - | - | - | - |
| rs13365225 | 8 | 36858483 | - | | 0.94 | 0.99 | -0.064 | -0.076 |
| rs13267382 | 8 | 117209548 | - | | 0.97 | 0.96 | 0.140 | 0.141 |
| rs11627032[8] | 14 | 93104072 | - | | 0.73 | 0.78 | -0.055 | -0.040 |
| chr17:29230520:D[9] | 17 | 29230520 | - | | 0.76 | - | - | - |
| rs745570 | 17 | 77781725 | - | | 0.93 | 0.92 | -0.068 | -0.073 |
| rs6507583 | 18 | 42399590 | - | | 0.96 | 0.98 | -0.057 | -0.056 |

[1] build 37 position

[2] Mean info score from IMPUTE2

[3] Correlation squared between the imputed and genotyped genotypes for 4123 samples in SEARCH

[4] Beta coefficient in the subset of SEARCH samples from the imputed data

[5] Beta coefficient in the subset of SEARCH samples from the genotyped data

[6] SNP rs186951, correlated with rs13162653, had better imputation quality and also reached $P<5x10^{-8}$ ($r^2$=0.91, $P$=2.1x10$^{-8}$).

[7] genotyped rs28912458 as an alternative (correlation between genotyped and imputed is 0.997, p combined in meta-analysis 6.263e-08)

[8] SNP rs11621587, correlated with rs11627032, had better imputation quality and also reached $P<5x10^{-8}$ ($r^2$=0.94, $P$=2.8x10$^{-8}$).

[9] Alternative SNP failed genotyping. SNP rs62070644,correlated with chr17:29230520:D, had better imputation quality and also reached $P<5x10^{-8}$ ($r^2$=0.98, $P$=4.5x10$^{-8}$).

**Supplementary Table 6**: Genotype-specific OR estimates for 15 novel risk loci, and analysis of heterogeneity in the per-allele ORs among studies, based on iCOGS data.

| Top variant | Chr[1] | Position[2] | Alleles[3] | Heterozygote OR (95% CI) | Homozygote OR (95% CI) | P value (2df) | P for departure from log additivity | Het P (Q) | $I^2$ |
|---|---|---|---|---|---|---|---|---|---|
| rs12405132 | 1 | 145644984 | C/T | 0.96 (0.93-0.99) | 0.89 (0.85-0.93) | $1.10x10^{-06}$ | 0.399 | 0.49 | 0 |
| rs12048493 | 1 | 149927034 | A/C | 1.06 (1.03-1.10) | 1.16 (1.10-1.23) | $1.03x10^{-08}$ | 0.517 | 0.15 | 18.87 |
| rs72755295 | 1 | 242034263 | A/G | 1.15 (1.08-1.21) | 1.62 (1.05-2.50) | $1.08x10^{-06}$ | 0.358 | 0.38 | 4.90 |
| rs6796502 | 3 | 46866866 | G/A | 0.93 (0.9-0.97) | 0.73 (0.62-0.85) | $7.50x10^{-07}$ | 0.049 | 0.46 | 0.38 |
| rs13162653 | 5 | 16187528 | G/T | 0.97 (0.93-1.01) | 0.89 (0.85-0.93) | $5.69x10^{-06}$ | 0.263 | 0.64 | 0 |
| rs2012709 | 5 | 32567732 | C/T | 1.05 (1.01-1.09) | 1.11 (1.06-1.16) | $1.03x10^{-05}$ | 0.916 | 0.12 | 21.03 |
| rs7707921 | 5 | 81538046 | A/T | 0.92 (0.86-0.99) | 0.86 (0.81-0.92) | $2.99x10^{-08}$ | 0.803 | 0.52 | 0 |
| rs9257408 | 6 | 28926220 | G/C | 1.05 (1.02-1.09) | 1.11 (1.06-1.16) | $2.93x10^{-06}$ | 0.898 | 0.04 | 30.15 |
| rs4593472 | 7 | 130667121 | C/T | 0.95 (0.92-0.97) | 0.92 (0.88-0.96) | $1.71x10^{-05}$ | 0.413 | 0.01 | 39.47 |
| rs13365225 | 8 | 36858483 | A/G | 0.94 (0.92-0.97) | 0.93 (0.85-1.01) | 0.000588 | 0.431 | 0.08 | 24.85 |
| rs13267382 | 8 | 117209548 | G/A | 1.06 (1.02-1.11) | 1.11 (1.06-1.16) | $2.24x10^{-05}$ | 0.471 | 0.95 | 0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| rs11627032 | 14 | 93104072 | T/C | 0.96 (0.92-0.99) | 0.85 (0.8-0.91) | $2.65x10^{-06}$ | 0.173 | 0.87 | 0 |
| chr17:29230520:D | 17 | 29230520 | GGT/G | 0.93 (0.90-0.96) | 0.89 (0.82-0.97) | $5.55x10^{-06}$ | 0.489 | 0.13 | 20.26 |
| rs745570 | 17 | 77781725 | A/G | 0.96 (0.93-0.99) | 0.9 (0.87-0.94) | $2.46x10^{-06}$ | 0.547 | 0.59 | 0 |
| rs6507583 | 18 | 42399590 | A/G | 0.91 (0.87-0.95) | 0.85 (0.69-1.04) | $7.39x10^{-06}$ | 0.805 | 0.94 | 0 |

[1] Chromosome

[2] Build 37 position

[3] Reference/effect allele (forward strand).

[4] OR for heterozygotes relative to reference allele homozygotes

[5] OR for homozygotes relative to effect allele homozygotes

[6] P-value for heterogeneity in the per-allele ORs among the iCOGS studies (Q-statistic)

[7] $I^2$ statistic for heterogeneity in the per-allele ORs among the iCOGS studies

**Supplementary Table 7**: Per allele ORs for DCIS vs invasive disease (based on 2470 dcis and 44,791 invasive cases in the iCOGS dataset).

| Top variant | Chr[1] | Position[2] | Alleles[3] | OR invasive (95% CI) | P invasive | OR dcis (95% CI) | P dcis | P invasive vs dcis |
|---|---|---|---|---|---|---|---|---|
| rs12405132 | 1 | 145644984 | C/T | 0.95 (0.93-0.97) | $1.22x10^{-07}$ | 0.97 (0.91-1.03) | 0.313 | 0.796 |
| rs12048493 | 1 | 149927034 | A/C | 1.07 (1.05-1.10) | $2.64x10^{-09}$ | 1.06 (0.99-1.14) | 0.103 | 0.89 |
| rs72755295 | 1 | 242034263 | A/G | 1.16 (1.1-1.23) | $1.08x10^{-07}$ | 1.02 (0.86-1.21) | 0.856 | 0.416 |
| rs6796502 | 3 | 46866866 | G/A | 0.91 (0.88-0.95) | $5.42x10^{-07}$ | 0.91 (0.82-1.02) | 0.107 | 0.674 |
| rs13162653 | 5 | 16187528 | G/T | 0.95 (0.93-0.97) | $3.18x10^{-06}$ | 0.95 (0.89-1.02) | 0.183 | 0.938 |
| rs2012709 | 5 | 32567732 | C/T | 1.05 (1.03-1.08) | $1.98x10^{-06}$ | 1.04 (0.97-1.11) | 0.267 | 0.741 |
| rs7707921 | 5 | 81538046 | A/T | 0.93 (0.91-0.95) | $1.28x10^{-08}$ | 0.93 (0.86-1) | 0.054 | 0.645 |
| rs9257408 | 6 | 28926220 | G/C | 1.06 (1.03-1.08) | $2.30x10^{-07}$ | 1.07 (1-1.14) | 0.038 | 0.706 |
| rs4593472 | 7 | 130667121 | C/T | 0.95 (0.93-0.97) | $2.67x10^{-06}$ | 0.97 (0.91-1.03) | 0.316 | 0.546 |
| rs13365225 | 8 | 36858483 | A/G | 0.95 (0.93-0.98) | 0.000356 | 0.92 (0.85-1) | 0.054 | 0.502 |
| rs13267382 | 8 | 117209548 | G/A | 1.05 (1.03-1.07) | $1.21x10^{-05}$ | 1.03 (0.96-1.09) | 0.416 | 0.456 |
| rs11627032 | 14 | 93104072 | T/C | 0.94 | $2.91x10^{-06}$ | 0.9 | 0.007 | 0.183 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | (0.92-0.96) | | (0.83-0.97) | | |
| chr17:29230520:D | 17 | 29230520 | GGT/G | 0.93 (0.91-0.96) | $6.36x10^{-07}$ | 0.96 (0.88-1.04) | 0.32 | 0.21 |
| rs745570 | 17 | 77781725 | A/G | 0.95 (0.93-0.97) | $1.34x10^{-07}$ | 0.99 (0.93-1.06) | 0.8 | 0.141 |
| rs6507583 | 18 | 42399590 | A/G | 0.91 (0.88-0.95) | $2.43x10^{-06}$ | 0.91 (0.81-1.03) | 0.13 | 0.939 |

[1] Chromosome

[2] Build 37 position

[3] Reference/effect allele (forward strand)

**Supplementary Table 8**: Per-allele ORs for ER- vs. ER+ disease (based on 7333 ER- cases and 27,078 ER+ cases in the iCOGS dataset).

| Top variant | Chr[1] | Position[2] | Alleles[3] | OR ER+ (95% CI) | P ER+ | OR ER- (95% CI) | P ER- | P ER+/ER- |
|---|---|---|---|---|---|---|---|---|
| rs12405132 | 1 | 145644984 | C/T | 0.93 (0.91-0.96) | $1.25x10^{-08}$ | 0.98 (0.94-1.02) | 0.3386 | 0.019 |
| rs12048493 | 1 | 149927034 | A/C | 1.09 (1.06-1.12) | $3.37x10^{-10}$ | 1.02 (0.98-1.06) | 0.292 | 0.010 |
| rs72755295 | 1 | 242034263 | A/G | 1.16 (1.09-1.24) | $4.04x10^{-06}$ | 1.21 (1.09-1.34) | 0.0004 | 0.599 |
| rs6796502 | 3 | 46866866 | G/A | 0.9 (0.87-0.94) | $1.25x10^{-06}$ | 0.94 (0.88-1.01) | 0.0950 | 0.070 |
| rs13162653 | 5 | 16187528 | G/T | 0.94 (0.92-0.97) | $1.75x10^{-05}$ | 0.96 (0.92-1) | 0.0517 | 0.388 |
| rs2012709 | 5 | 32567732 | C/T | 1.05 (1.03-1.08) | $7.27x10^{-05}$ | 1.04 (1-1.08) | 0.0784 | 0.684 |
| rs7707921 | 5 | 81538046 | A/T | 0.92 (0.89-0.95) | $5.00x10^{-09}$ | 0.97 (0.92-1.01) | 0.1380 | 0.062 |
| rs9257408 | 6 | 28926220 | G/C | 1.05 (1.03-1.08) | $5.07x10^{-05}$ | 1.05 (1.01-1.1) | 0.0095 | 0.867 |
| rs4593472 | 7 | 130667121 | C/T | 0.94 (0.92-0.96) | $3.57x10^{-07}$ | 0.99 (0.95-1.03) | 0.6806 | 0.046 |
| rs13365225 | 8 | 36858483 | A/G | 0.95 (0.92-0.98) | 0.00062 | 0.93 (0.88-0.98) | 0.0034 | 0.608 |
| rs13267382 | 8 | 117209548 | G/A | 1.05 (1.02-1.07) | $9.57x10^{-05}$ | 1.06 (1.02-1.1) | 0.0043 | 0.851 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| rs11627032 | 14 | 93104072 | T/C | 0.95 (0.92-0.98) | 0.00077 | 0.92 (0.87-0.96) | 0.0007 | 0.426 |
| chr17:29230520:D | 17 | 29230520 | GGT/G | 0.92 (0.89-0.95) | $1.43x10^{-06}$ | 0.93 (0.88-0.98) | 0.008 | 0.781 |
| rs745570 | 17 | 77781725 | A/G | 0.94 (0.92-0.96) | $4.02x10^{-07}$ | 0.95 (0.91-0.99) | 0.0097 | 0.691 |
| rs6507583 | 18 | 42399590 | A/G | 0.9 (0.86-0.94) | $7.60x10^{-06}$ | 0.97 (0.9-1.05) | 0.4315 | 0.036 |

[1] Chromosome

[2] Build 37 position

[3] Reference/effect allele (forward strand)

**Supplementary Table 9:** Per-allele ORs by age at diagnosis ( age categories <40: 3987,40-50 : 9714, 50-60 :13,313 , >=60 : 15,176).

| Top variant | Chr[1] | Position[2] | Alleles[3] | Per-allele OR (95% CI) by age at diagnosis | | | | P-value for trend |
|---|---|---|---|---|---|---|---|---|
| | | | | <40 | 40-49 | 50-59 | 60+ | |
| rs12405132 | 1 | 145644984 | C/T | 0.96 (0.91-1.01) | 0.94 (0.9-0.97) | 0.96 (0.93-0.99) | 0.94 (0.92-0.97) | 0.998 |
| rs12048493 | 1 | 149927034 | A/C | 1.07 (1-1.13) | 1.11 (1.07-1.15) | 1.06 (1.02-1.09) | 1.07 (1.04-1.10) | 0.133 |
| rs72755295 | 1 | 242034263 | A/G | 1.21 (1.05-1.39) | 1.19 (1.09-1.31) | 1.13 (1.05-1.22) | 1.16 (1.08-1.25) | 0.852 |
| rs6796502 | 3 | 46866866 | G/A | 0.91 (0.84-1) | 0.88 (0.83-0.94) | 0.91 (0.87-0.96) | 0.93 (0.89-0.98) | 0.522 |
| rs13162653 | 5 | 16187528 | G/T | 0.89 (0.84-0.95) | 0.93 (0.9-0.97) | 0.94 (0.91-0.97) | 0.96 (0.93-0.99) | 0.007 |
| rs2012709 | 5 | 32567732 | C/T | 1.04 (0.98-1.1) | 1.05 (1.01-1.09) | 1.05 (1.02-1.08) | 1.05 (1.02-1.08) | 0.528 |
| rs7707921 | 5 | 81538046 | A/T | 0.96 (0.9-1.02) | 0.9 (0.86-0.94) | 0.95 (0.91-0.98) | 0.92 (0.89-0.95) | 0.999 |
| rs9257408 | 6 | 28926220 | G/C | 1.01 (0.96-1.07) | 1.06 (1.02-1.09) | 1.04 (1.01-1.07) | 1.07 (1.04-1.1) | 0.774 |
| rs4593472 | 7 | 130667121 | C/T | 0.97 (0.92-1.02) | 0.95 (0.92-0.99) | 0.94 (0.92-0.97) | 0.96 (0.93-0.98) | 0.867 |
| rs13365225 | 8 | 36858483 | A/G | 0.9 (0.84-0.96) | 0.96 (0.91-1) | 0.93 (0.9-0.97) | 0.97 (0.94-1.01) | 0.492 |
| rs13267382 | 8 | 117209548 | G/A | 1.06 (1.01-1.12) | 1.08 (1.05-1.12) | 1.05 (1.02-1.08) | 1.04 (1.01-1.07) | 0.332 |
| rs11627032 | 14 | 93104072 | T/C | 0.93 | 0.93 | 0.95 | 0.94 | 0.464 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | (0.87-0.99) | (0.89-0.97) | (0.92-0.99) | (0.91-0.97) | |
| chr17:29230520:D | 17 | 29230520 | GGT/G | 0.89 (0.83-0.96) | 0.92 (0.88-0.97) | 0.95 (0.91-0.99) | 0.92 (0.89-0.96) | 0.52 |
| rs745570 | 17 | 77781725 | A/G | 0.95 (0.91-1) | 0.95 (0.92-0.98) | 0.95 (0.92-0.98) | 0.96 (0.93-0.99) | 0.704 |
| rs6507583 | 18 | 42399590 | A/G | 1.02 (0.92-1.12) | 0.92 (0.86-0.98) | 0.91 (0.86-0.96) | 0.88 (0.84-0.93) | 0.006 |

[1] Chromosome

[2] Build 37 position

[3] Reference/effect allele (forward strand)

## Supplementary Note

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