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

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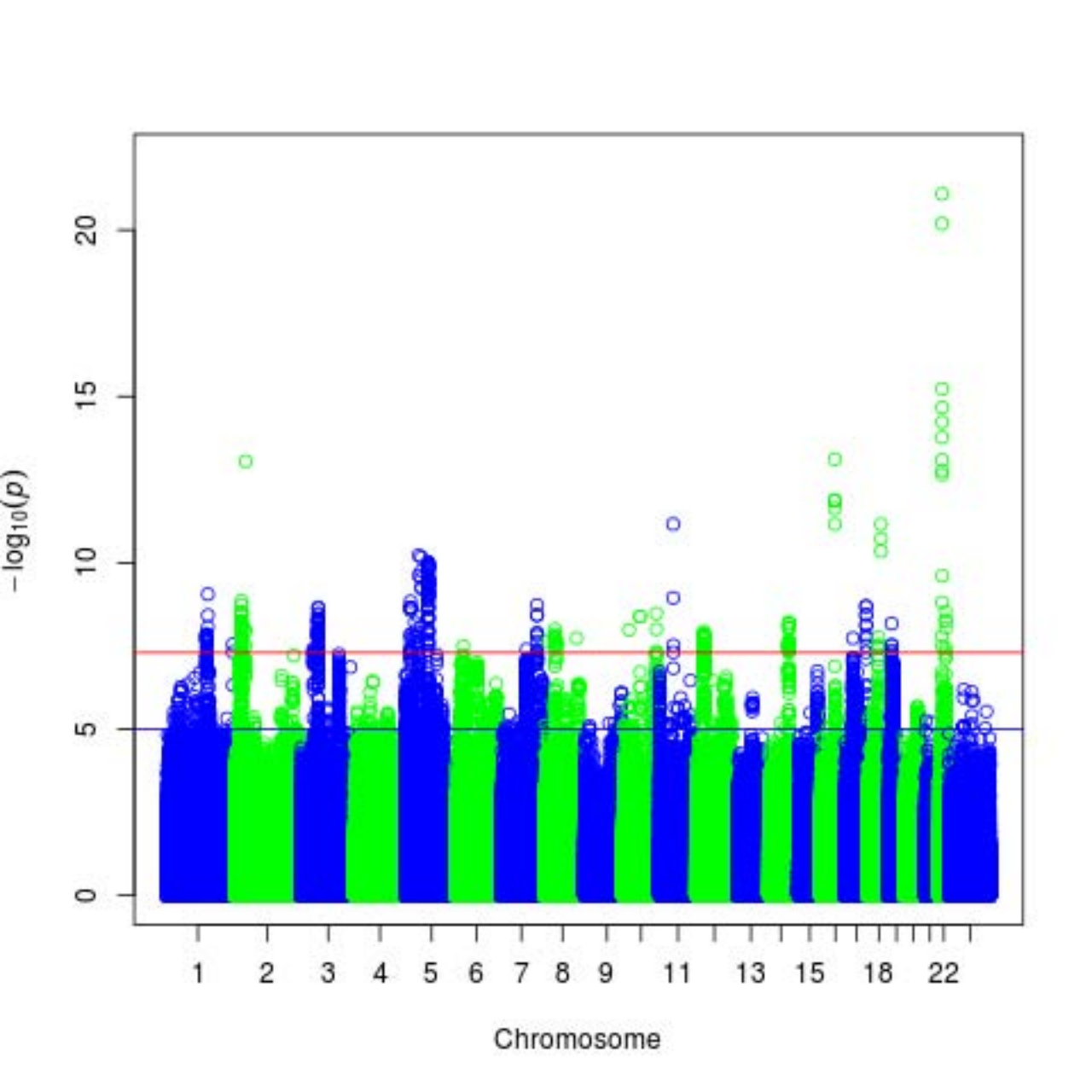
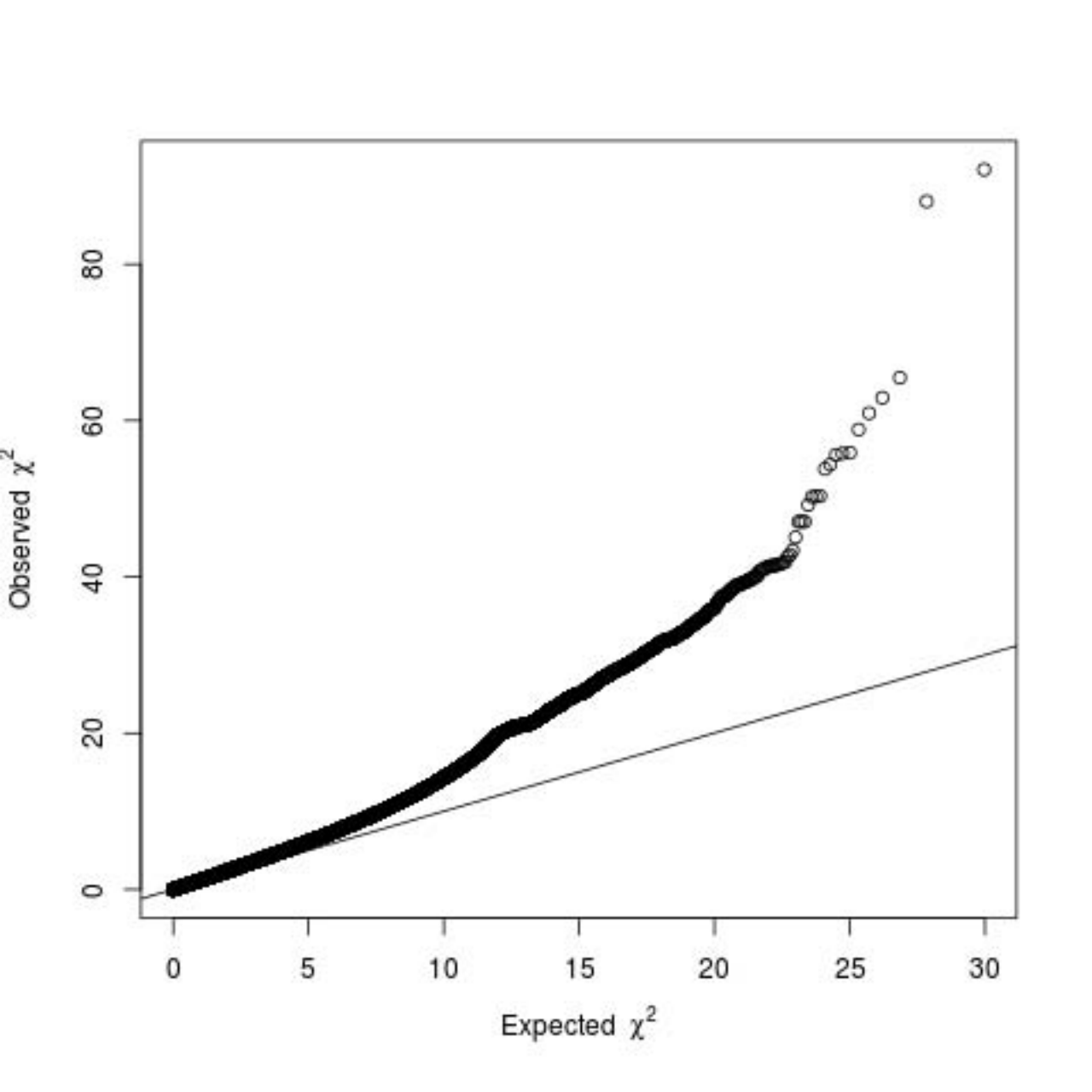
Supplementary Material

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 $P=10^{-5}$.

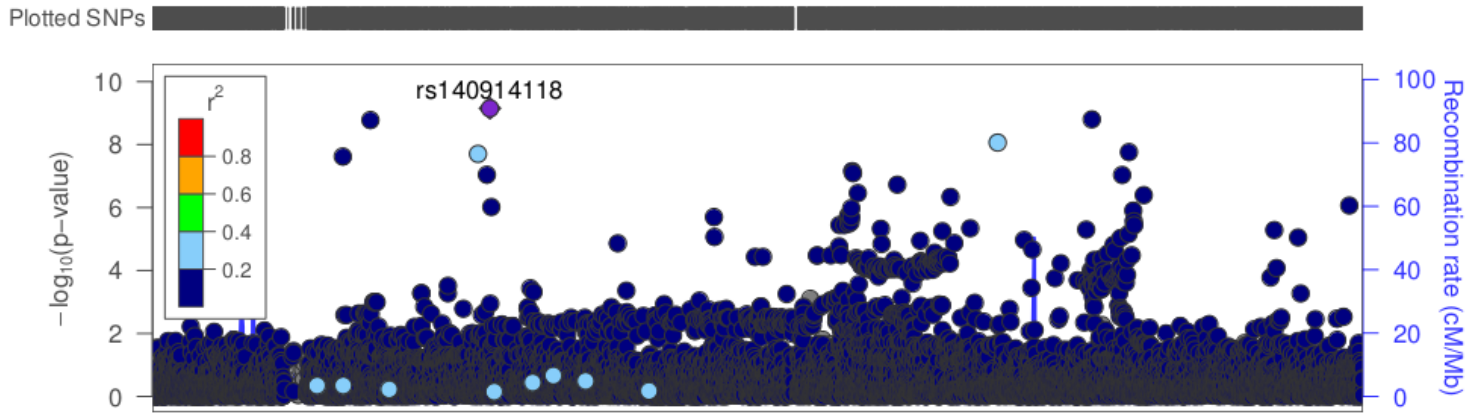

$-\log_{10}(p)$
0
5
10
15
20
1
2
3
4
5
6
7
8
9
11
13
15
18
22
Chromosome

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.

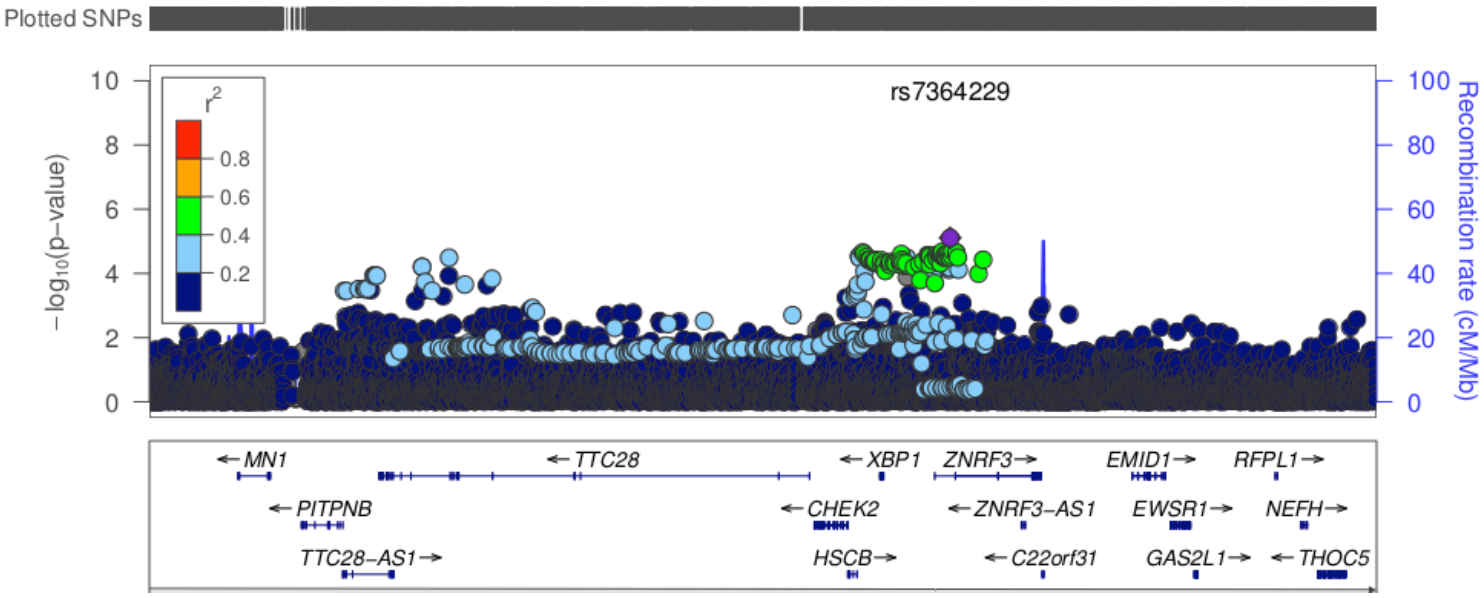

Observed χ^2
0
20
40
60
80
0
5
10
15
20
25
30
Expected χ^2

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)

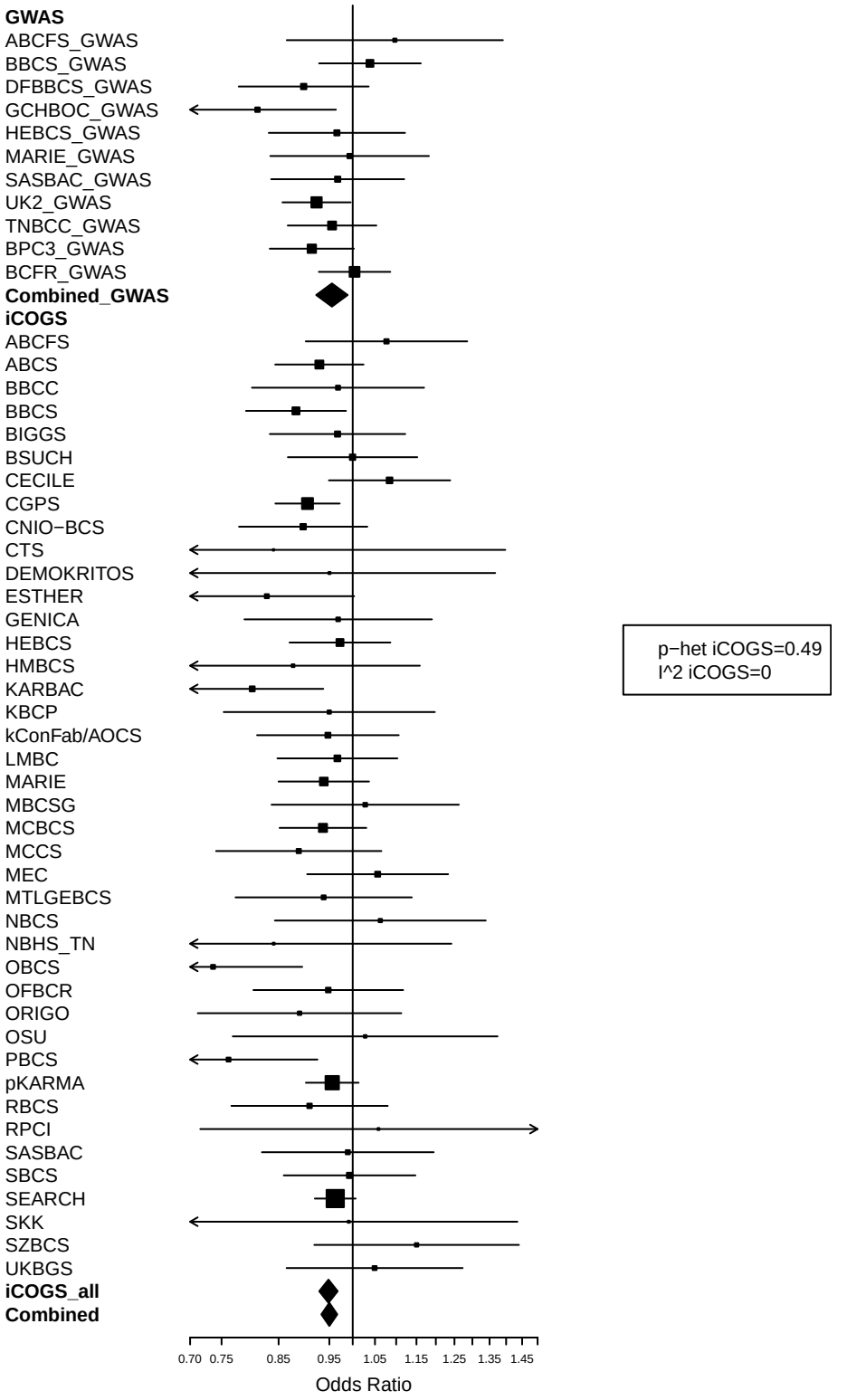

Plotted SNPs
rs140914118
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
0
2
4
6
8
10
0
20
40
60
80
100

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
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MTLGEBCS
NBCS
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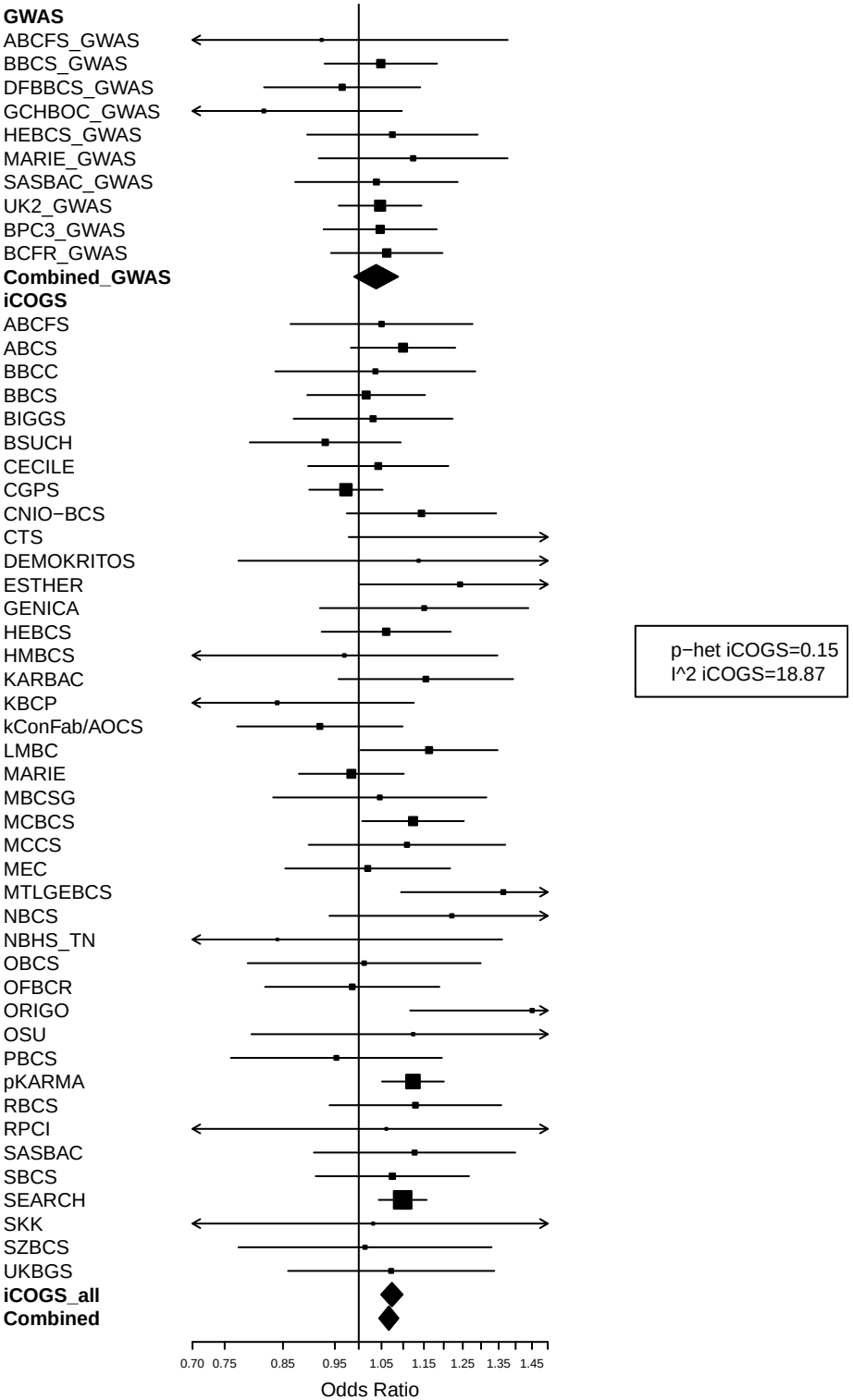
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
p−het iCOGS=0.49
I^2 iCOGS=0
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio

rs12048493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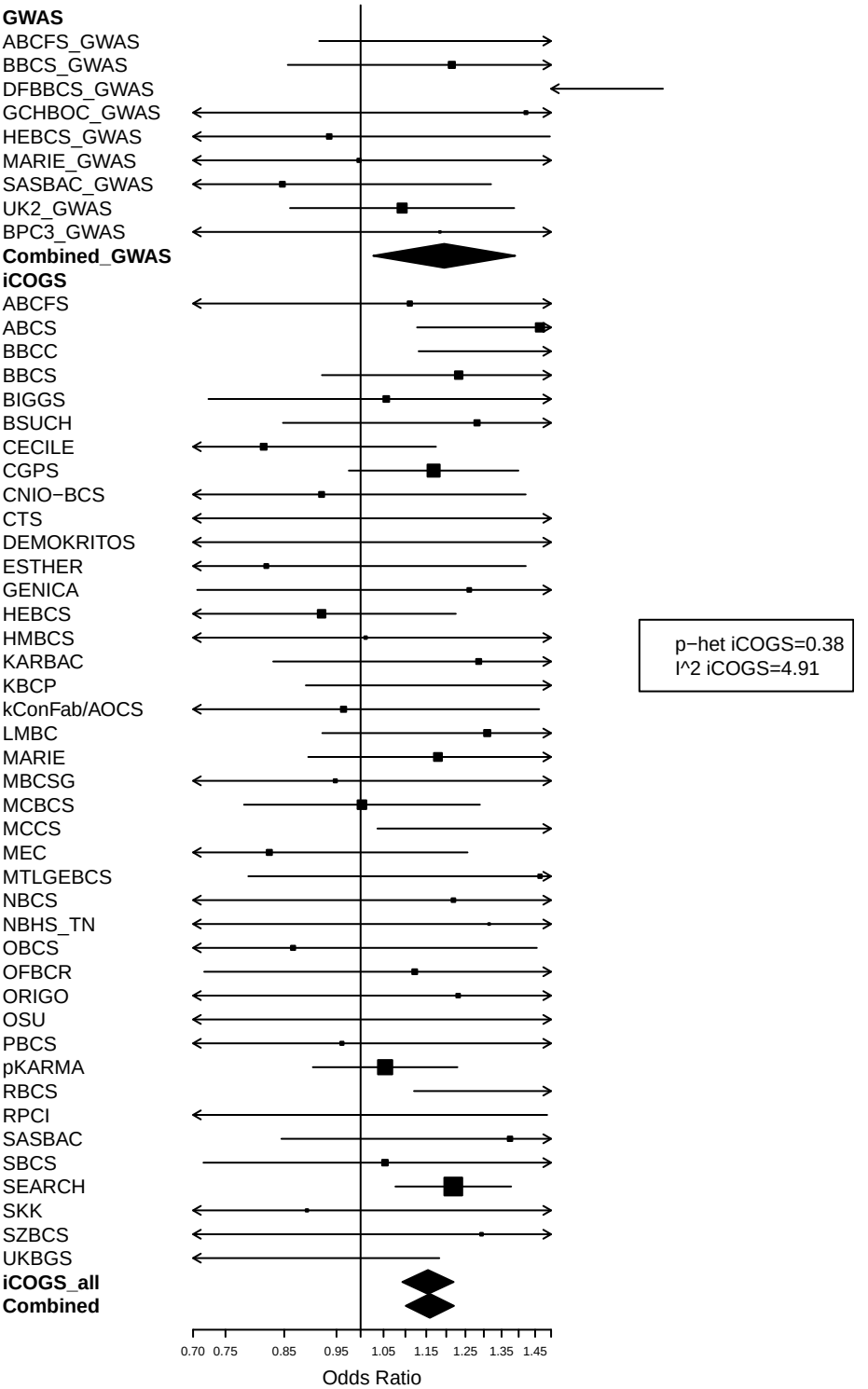
BBCS_GWAS
DFBBCS_GWAS
GCHBOC_GWAS
HEBCS_GWAS
MARIE_GWAS
SASBAC_GWAS
UK2_GWAS
BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
CNIO−BCS
CTS
DEMOKRITOS
ESTHER
GENICA
HEBCS
HMBCS
KARBAC
KBCP
kConFab/AOCS
LMBC
MARIE
MBCSG
MCBCS
MCCS
MEC
MTLGEBCS
NBCS
NBHS_TN
OBCS
OFBCR
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=0.15
I^2 iCOGS=18.87

rs72755295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HEBCS_GWAS
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BPC3_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
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OBCS
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
p−het iCOGS=0.38
I^2 iCOGS=4.91
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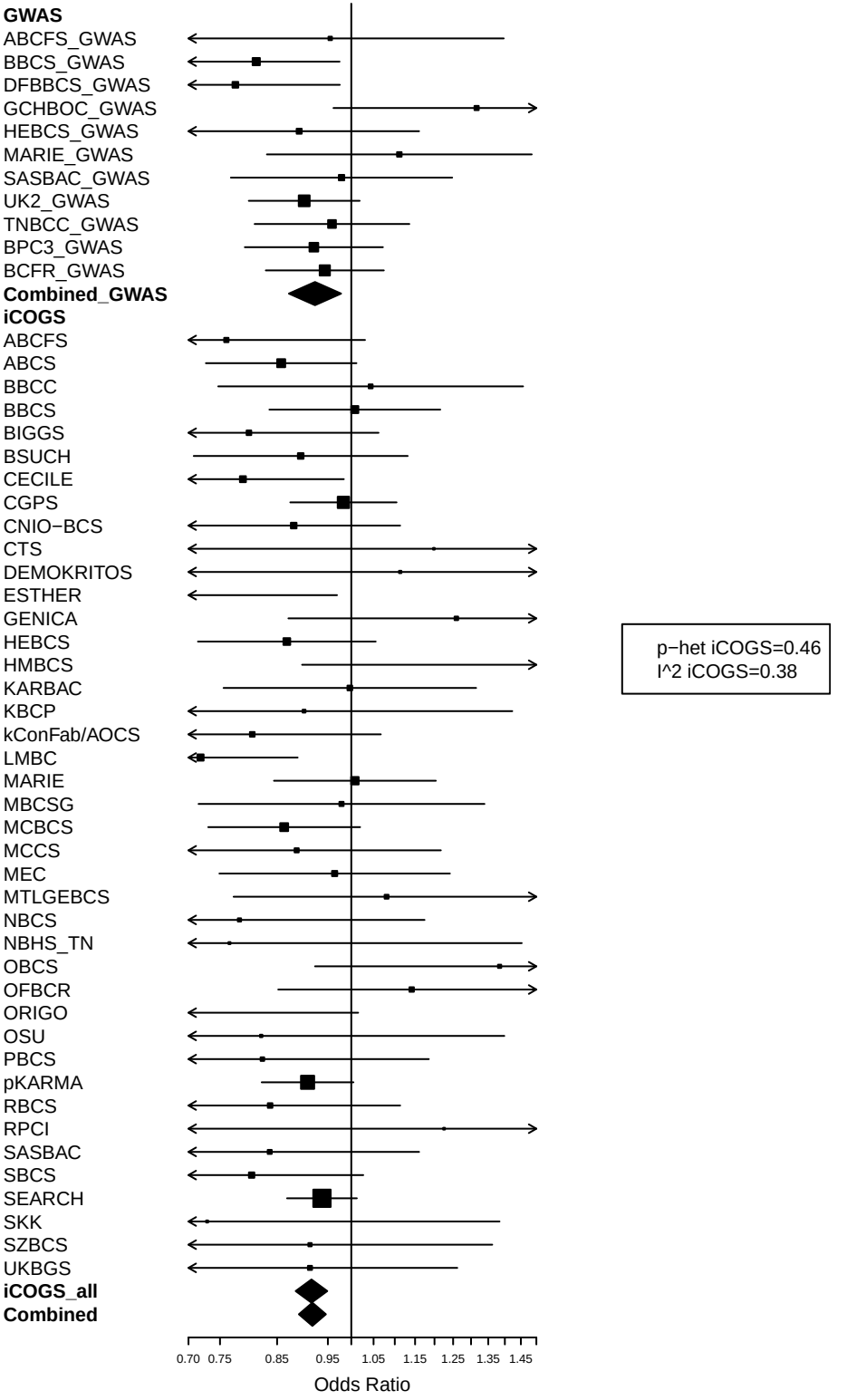
Odds Ratio

rs6796502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TNBCC_GWAS
BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
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CTS
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KBCP
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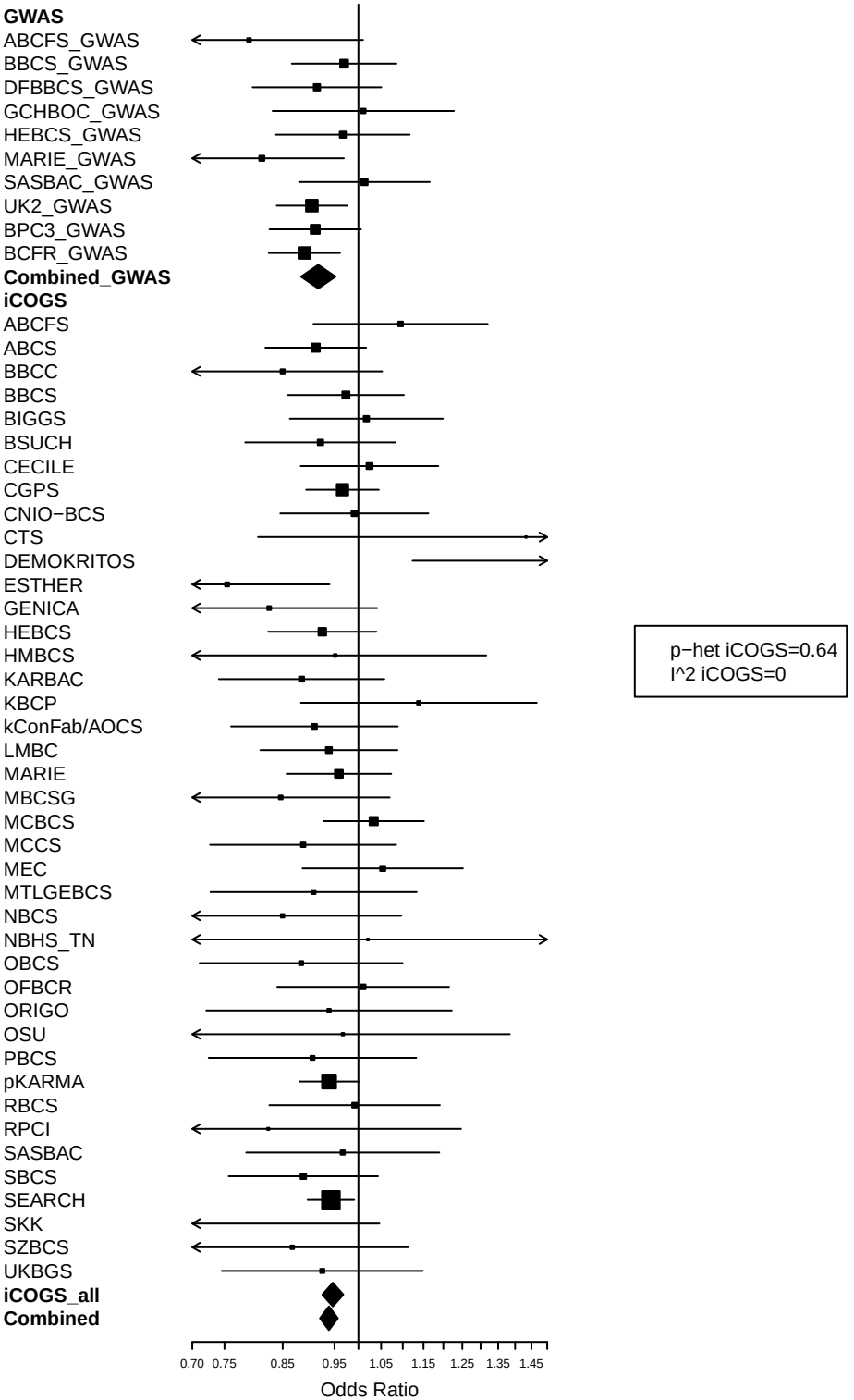
NBCS
NBHS_TN
OBCS
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
p−het iCOGS=0.46
I^2 iCOGS=0.38

rs13162653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SASBAC_GWAS
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BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
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CGPS
CNIO−BCS
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DEMOKRITOS
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KARBAC
KBCP
kConFab/AOCS
LMBC
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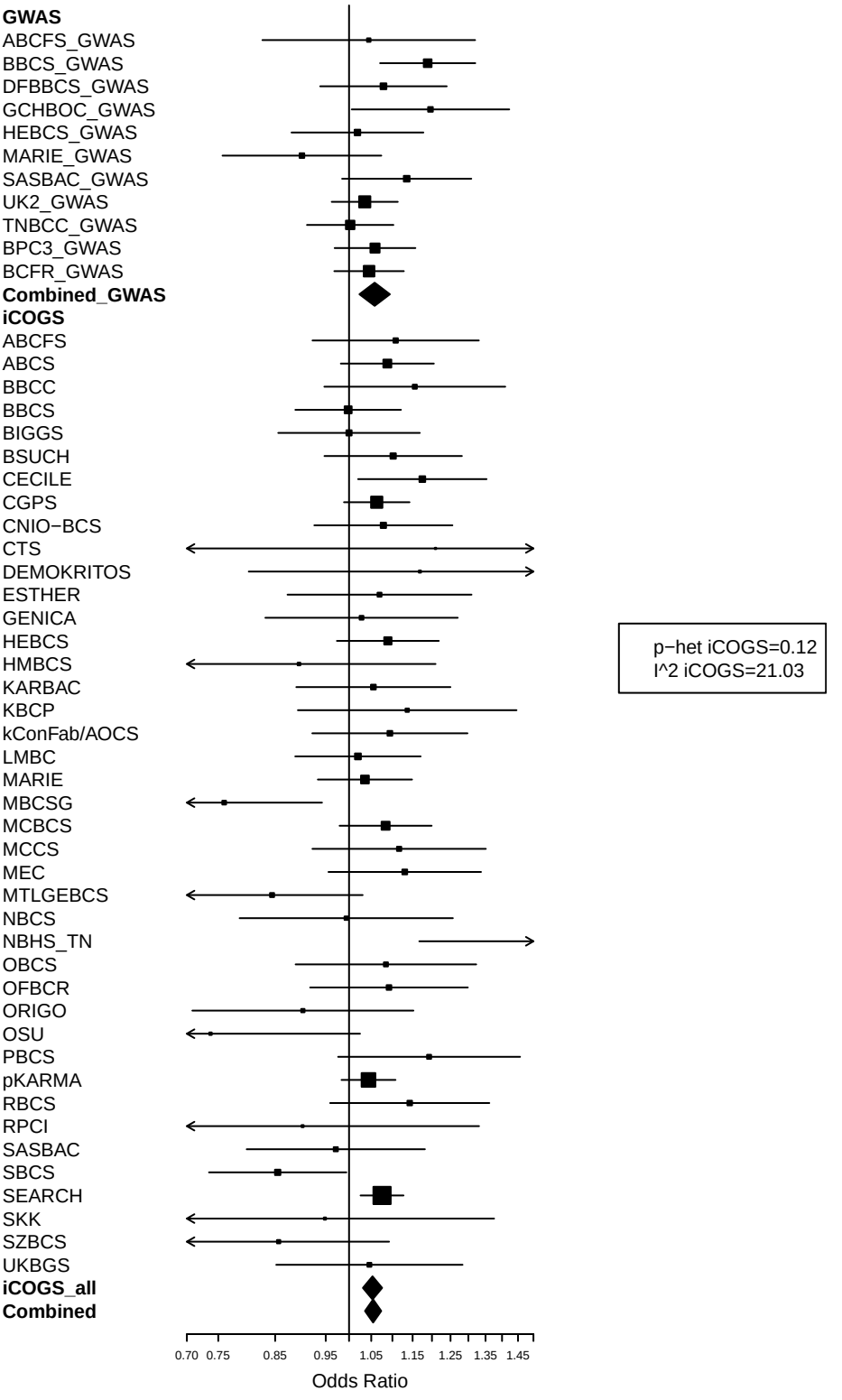
OBCS
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
p−het iCOGS=0.64
I^2 iCOGS=0
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio

rs2012709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UK2_GWAS
TNBCC_GWAS
BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
CNIO−BCS
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ESTHER
GENICA
HEBCS
HMBCS
KARBAC
KBCP
kConFab/AOCS
LMBC
MARIE
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MCBCS
MCCS
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NBHS_TN
OBCS
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
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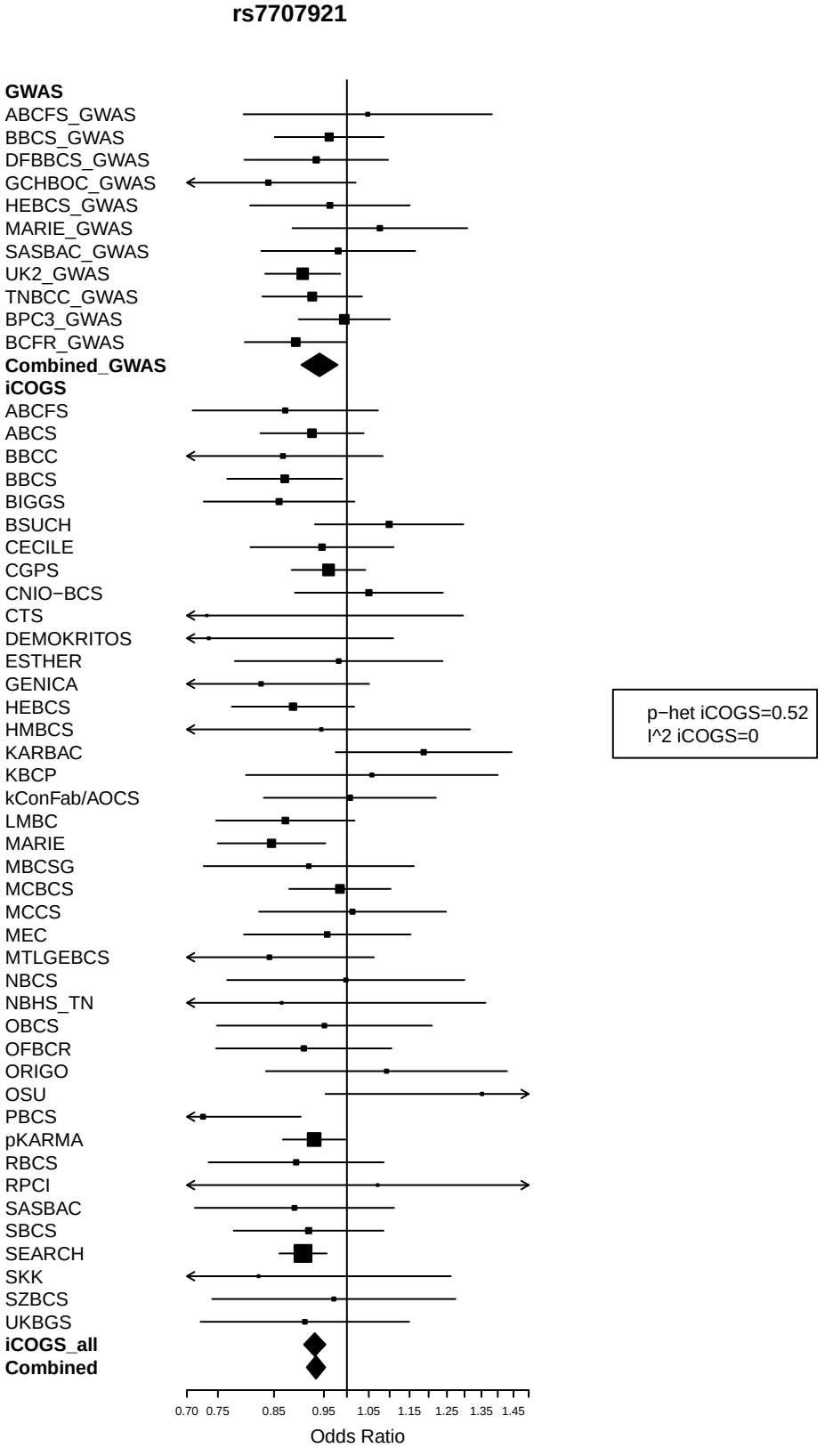
Odds Ratio
p−het iCOGS=0.12
I^2 iCOGS=21.03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UK2_GWAS
TNBCC_GWAS
BPC3_GWAS
BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
ABCS
BBCC
BBCS
BIGGS
BSUCH
CECILE
CGPS
CNIO−BCS
CTS
DEMOKRITOS
ESTHER
GENICA
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HMBCS
KARBAC
KBCP
kConFab/AOCS
LMBC
MARIE
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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
p−het iCOGS=0.52
I^2 iCOGS=0
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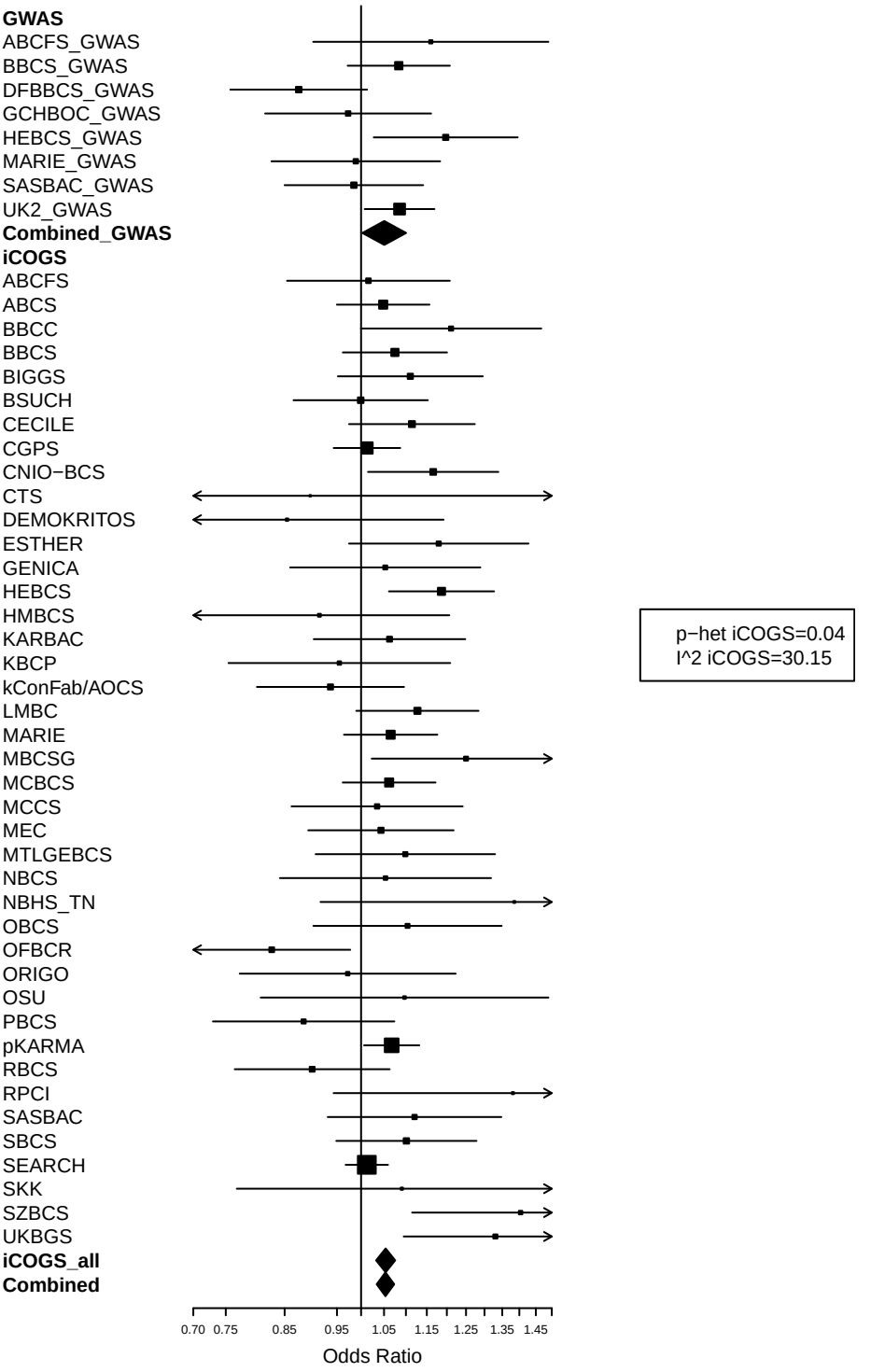
Odds Ratio

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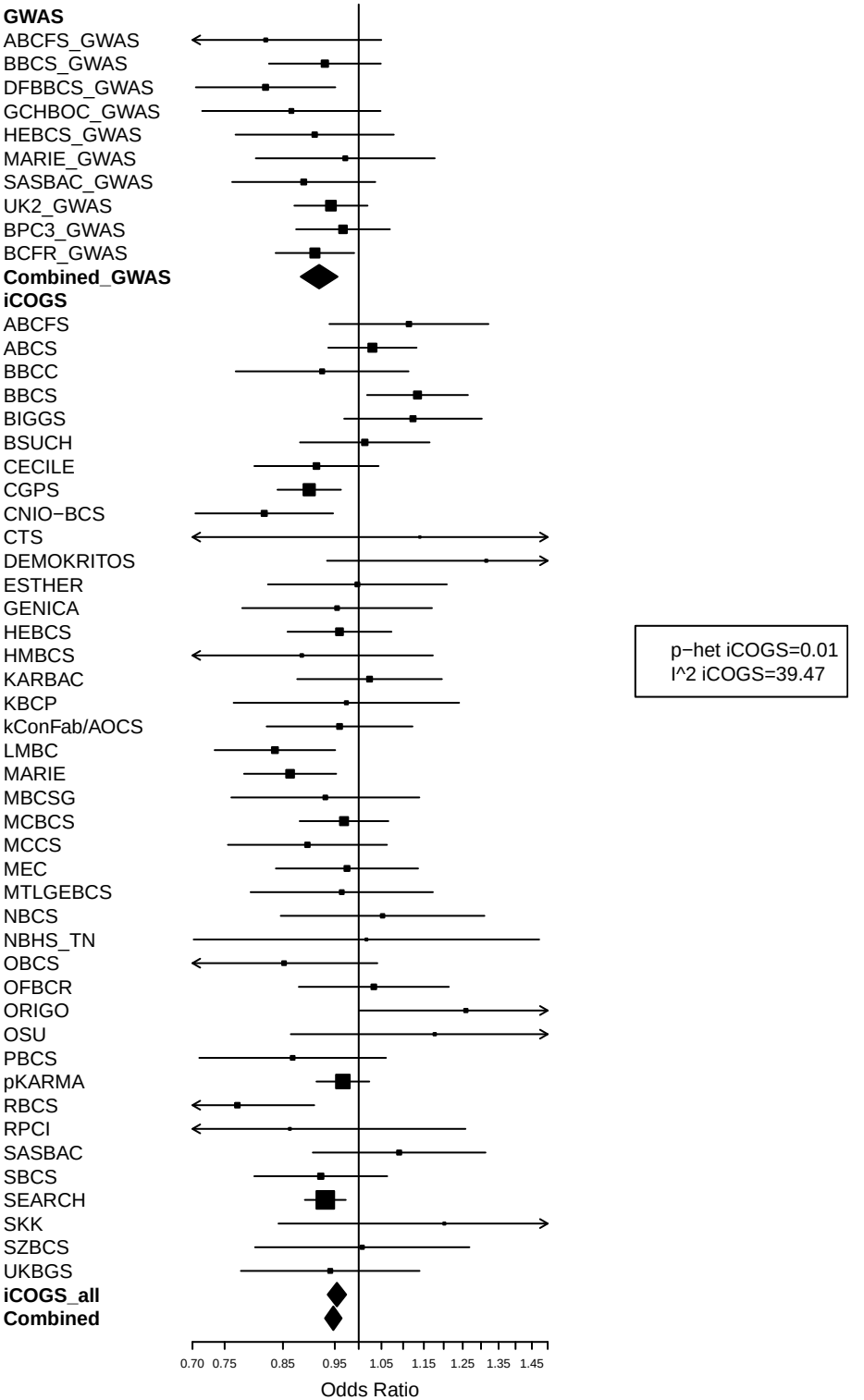
NBHS_TN
OBCS
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
p−het iCOGS=0.04
I^2 iCOGS=30.15

rs4593472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BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
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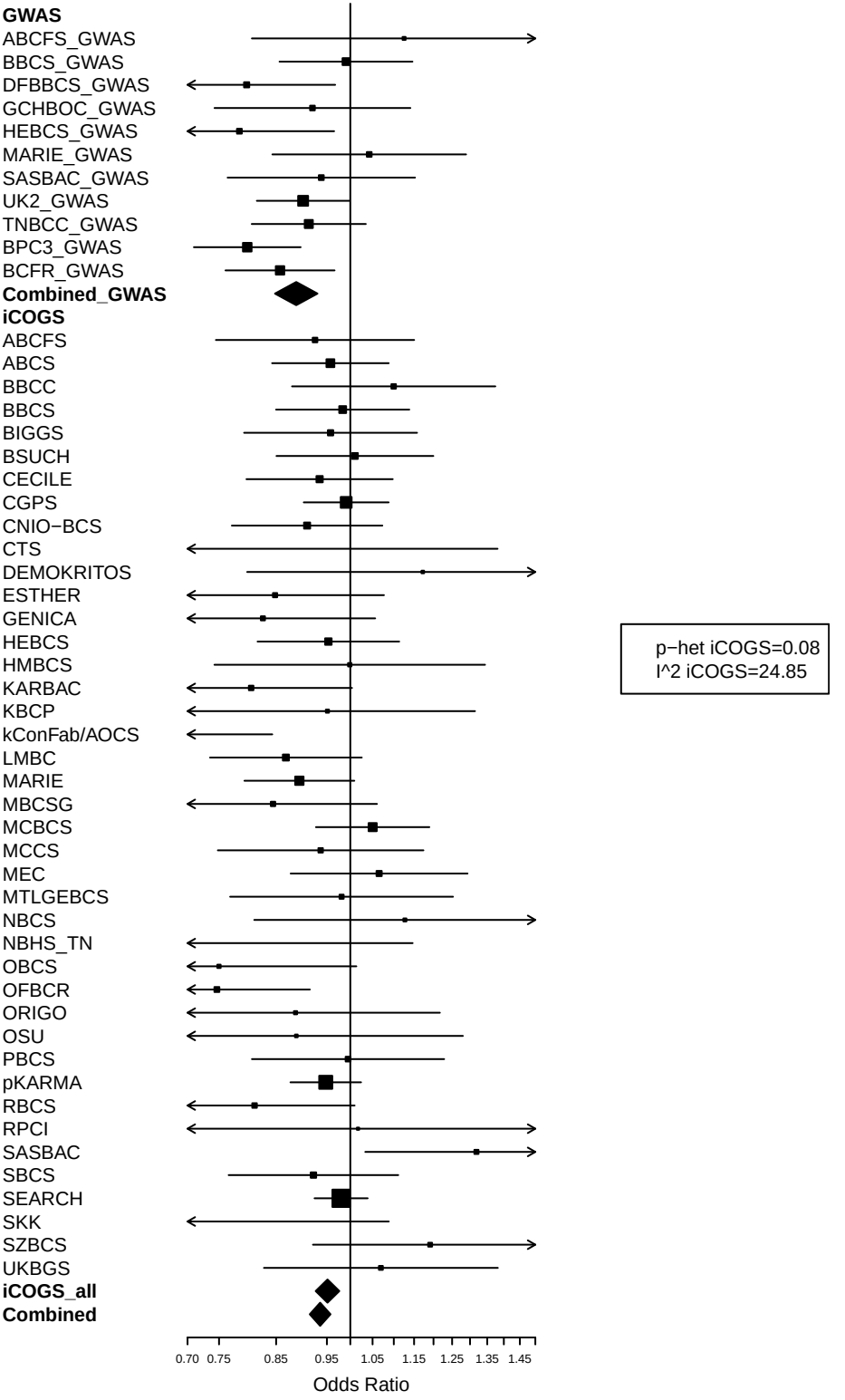
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
p−het iCOGS=0.01
I^2 iCOGS=39.47

rs13365225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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
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LMBC
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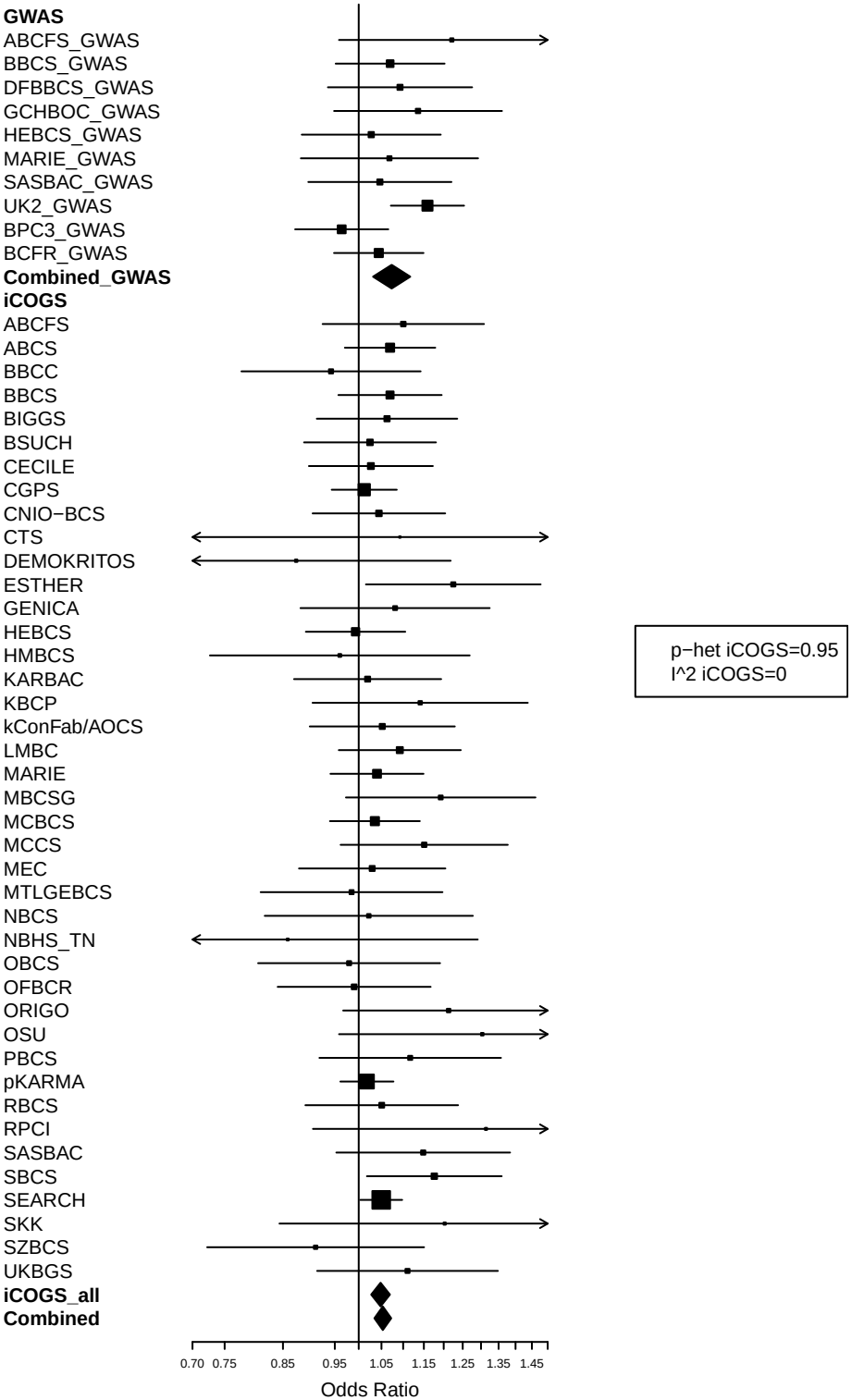
OBCS
OFBCR
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
p−het iCOGS=0.08
I^2 iCOGS=24.85

rs13267382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BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
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BBCC
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DEMOKRITOS
ESTHER
GENICA
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NBHS_TN
OBCS
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ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
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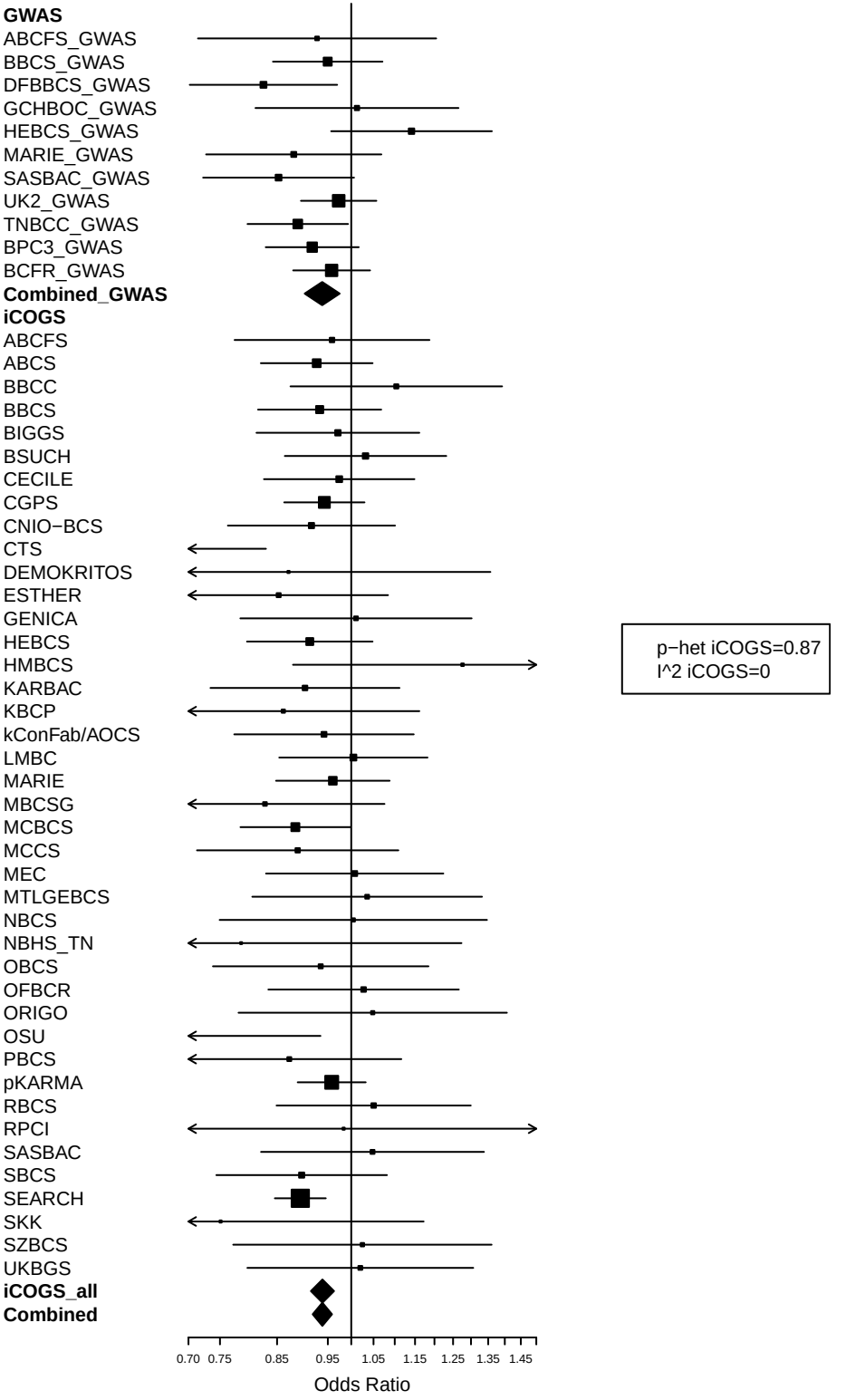
Odds Ratio
p−het iCOGS=0.95
I^2 iCOGS=0

rs11627032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Combined_GWAS
iCOGS
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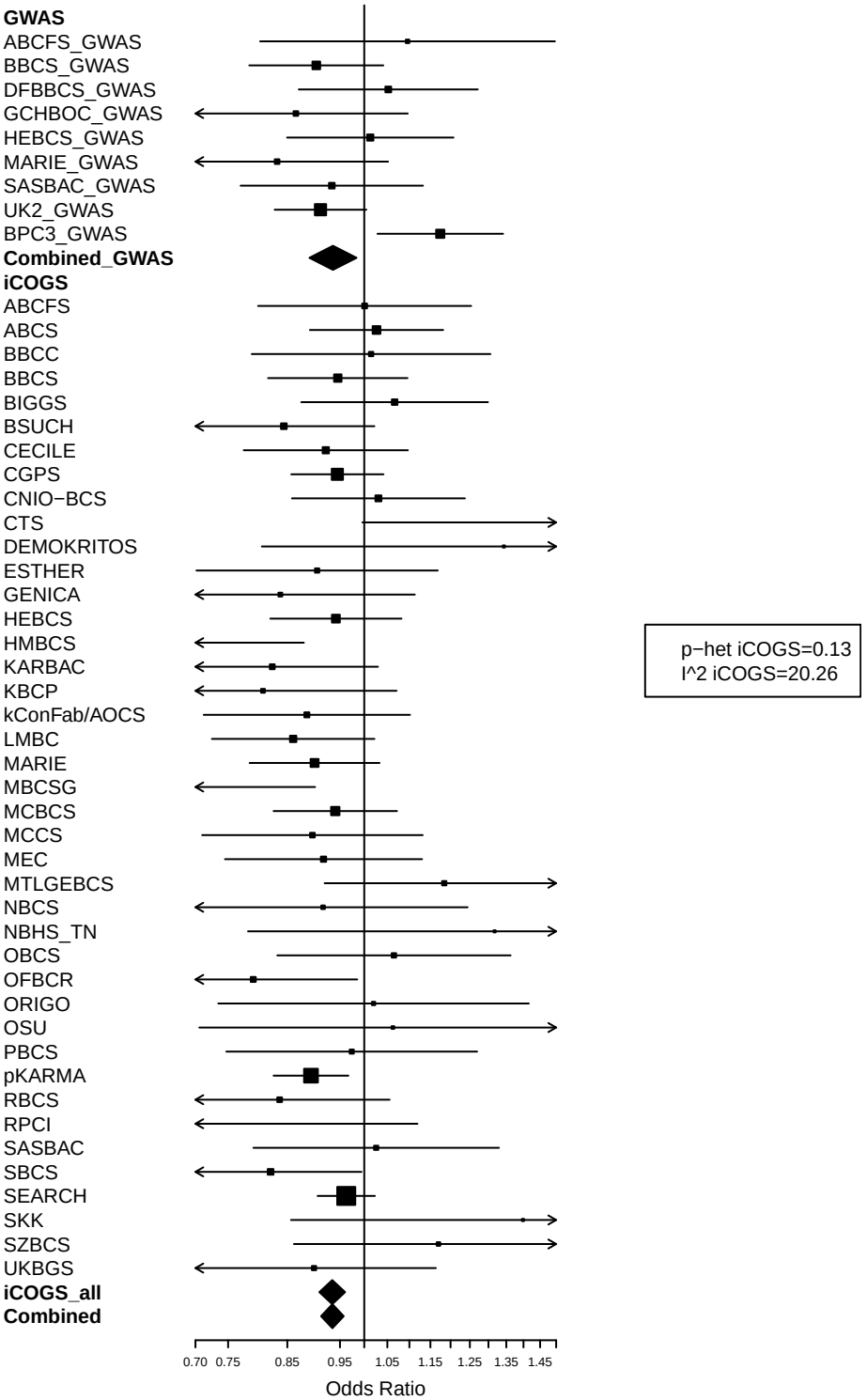
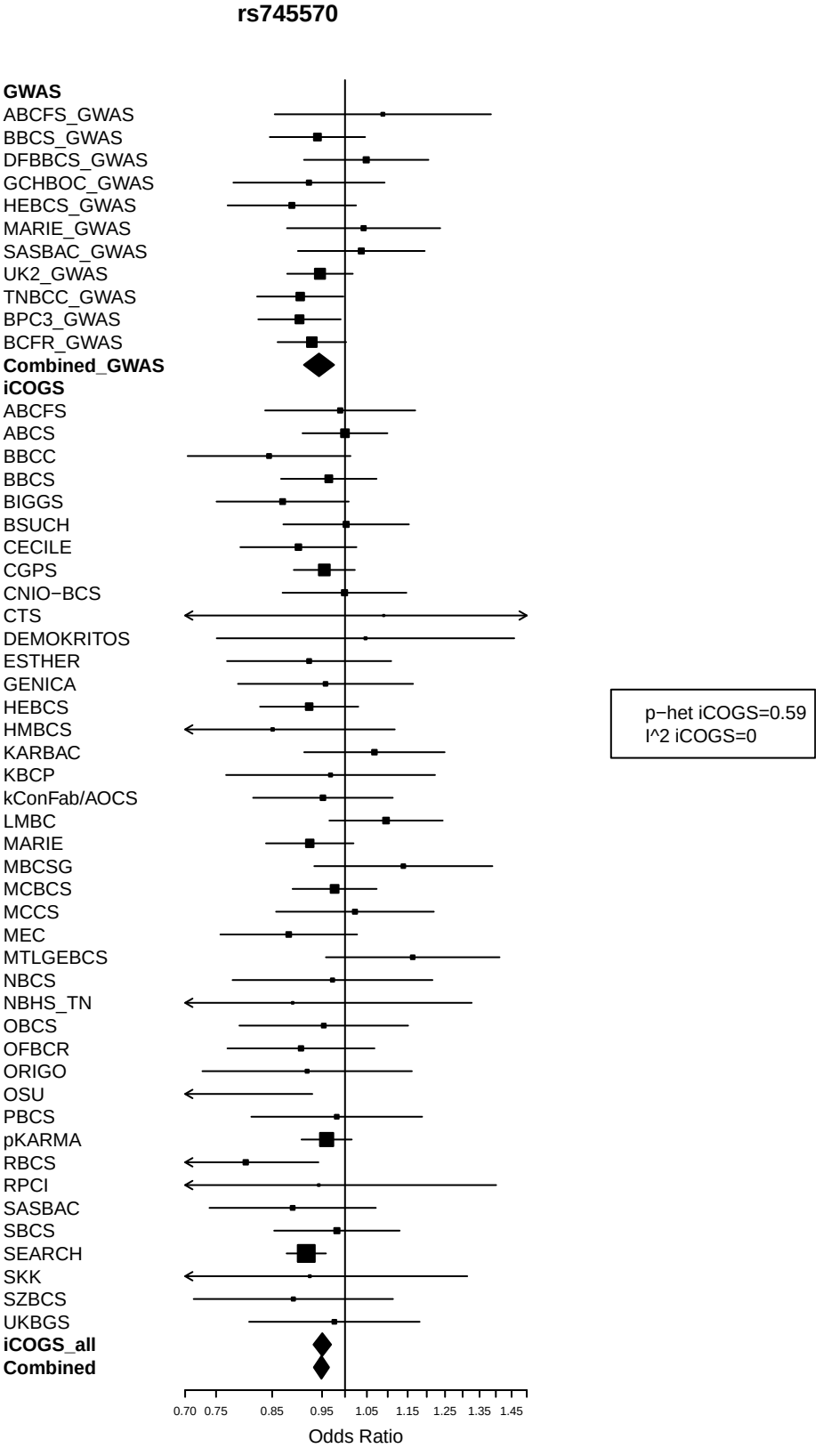
ORIGO
OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
p−het iCOGS=0.87
I^2 iCOGS=0

chr17:29230520:D

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BCFR_GWAS
Combined_GWAS
iCOGS
ABCFS
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OSU
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
p−het iCOGS=0.59
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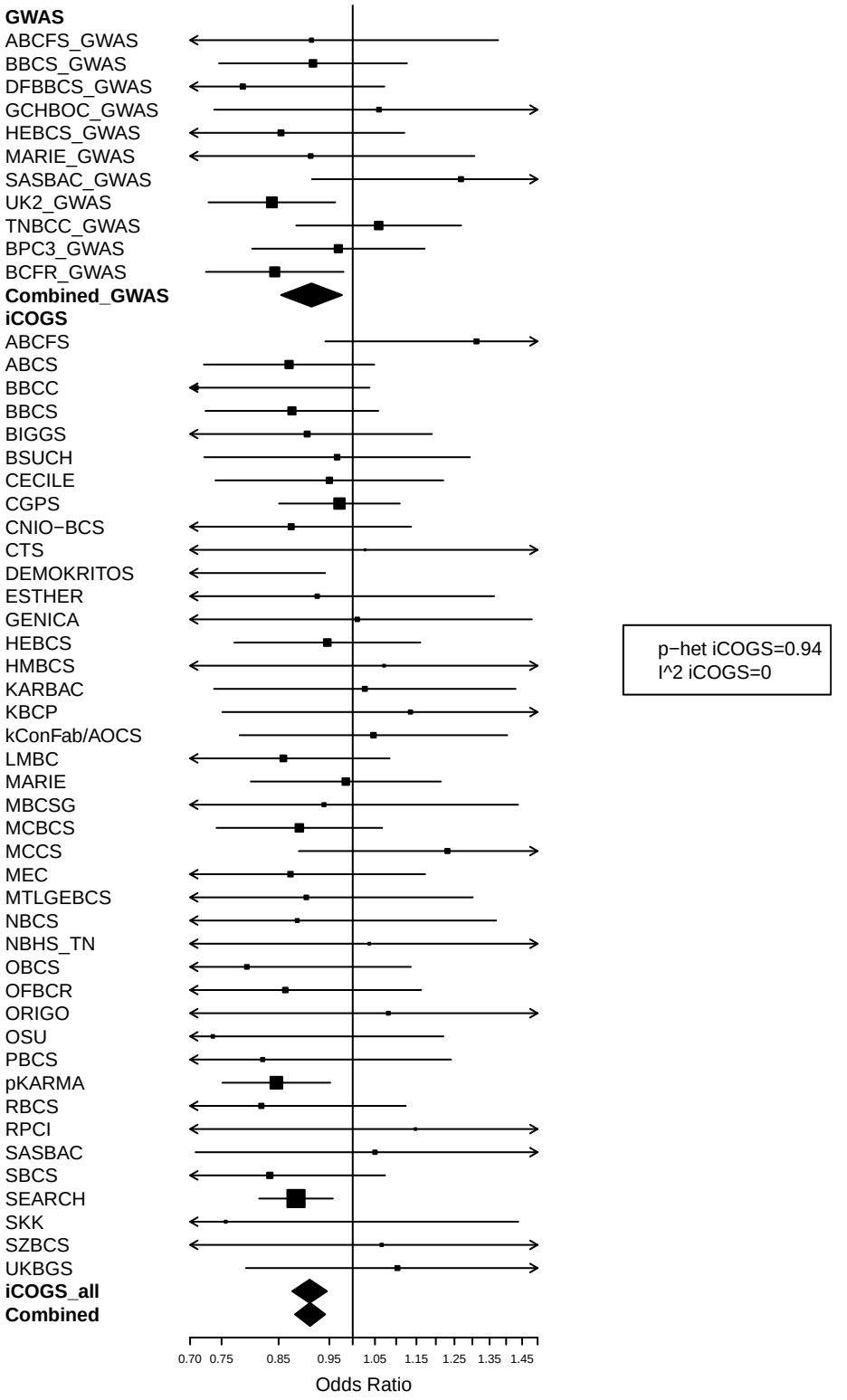
Odds Ratio

rs6507583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GCHBOC_GWAS
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MARIE_GWAS
SASBAC_GWAS
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BCFR_GWAS
Combined_GWAS
iCOGS
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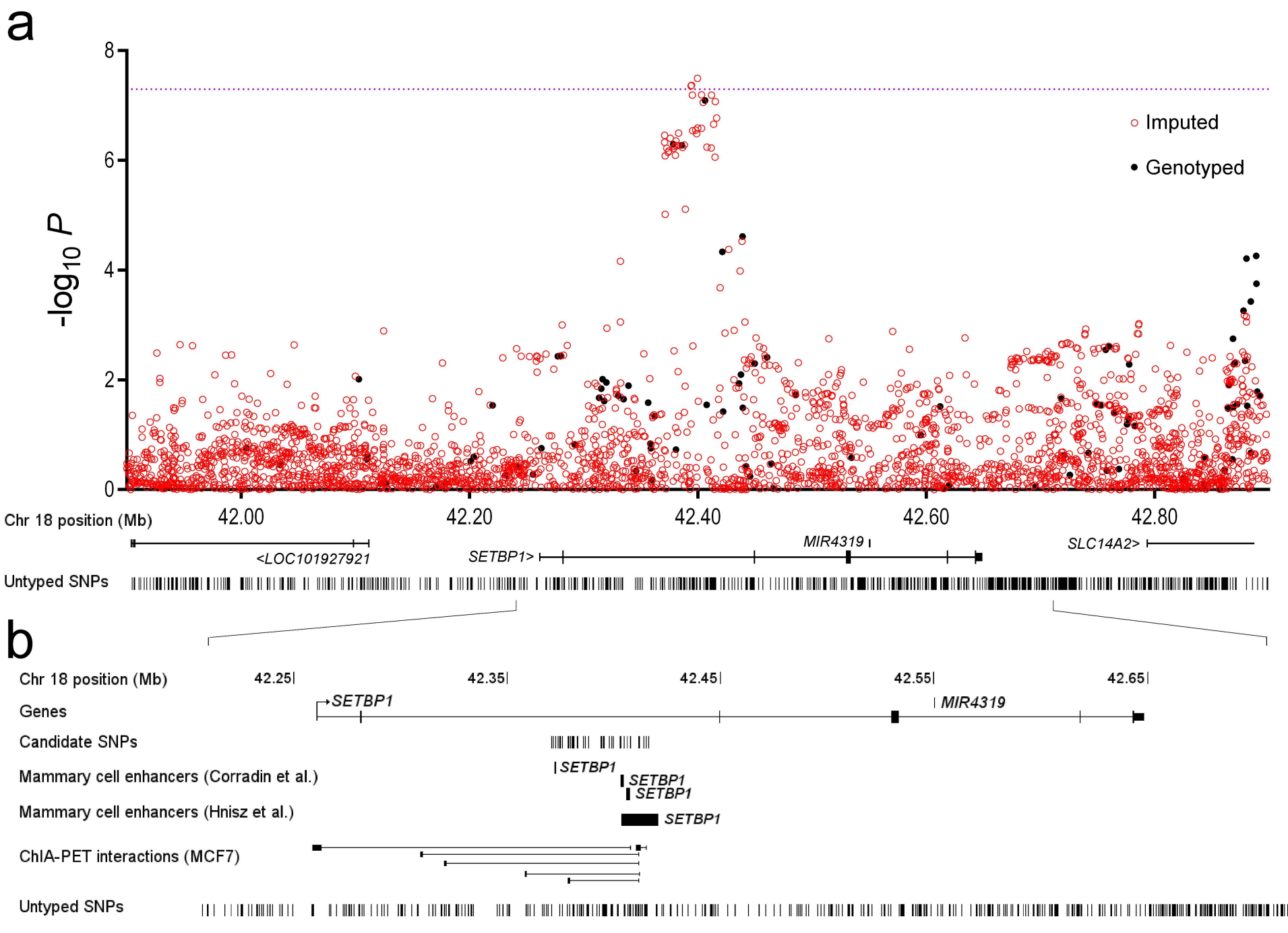
PBCS
pKARMA
RBCS
RPCI
SASBAC
SBCS
SEARCH
SKK
SZBCS
UKBGS
iCOGS_all
Combined
0.70 0.75 0.85 0.95 1.05 1.15 1.25 1.35 1.45
Odds Ratio
p−het iCOGS=0.94
I^2 iCOGS=0

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
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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)	3.06×10^{-07}	4.30×10^{-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)	5.37×10^{-22}	1.87×10^{-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)	1.73×10^{-06}	4.51×10^{-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)	1.98×10^{-08}	4.93×10^{-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)	5.46×10^{-07}	0.49	1	0.86(0.84-0.88)	2.26×10^{-37}	1.90×10^{-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)	2.35×10^{-10}	5.46×10^{-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)	8.05×10^{-09}	1.74×10^{-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)	1.05×10^{-17}	3.91×10^{-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)	5.67×10^{-08}	3.18×10^{-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)	2.86×10^{-06}	1.11×10^{-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)	$1.14x10^{-09}$	$1.00x10^{-10}$

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)	$9.52x10^{-46}$	$1.48x10^{-46}$

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)	3.82×10^{-10}	2.18×10^{-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)	5.08×10^{-07}	1.30×10^{-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)	3.18×10^{-12}	4.81×10^{-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)	3.49×10^{-09}	2.81×10^{-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)	8.44×10^{-06}	3.35×10^{-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)	2.81×10^{-10}	1.64×10^{-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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