Identification of six new susceptibility loci for invasive epithelial ovarian cancer

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Genome-wide association studies (GWAS) have identified 12 epithelial ovarian cancer (EOC) susceptibility alleles. The pattern of association at these loci is consistent in *BRCA1* and *BRCA2* mutation carriers who are at high EOC risk. After imputation to the 1000 Genomes Project data, we assessed associations of 11 million genetic variants with EOC risk from 15,397 cases unselected for family history and 30,816 controls, 15,252 *BRCA1* mutation carriers and 8,211 *BRCA2* mutation carriers (3,096 with ovarian cancer), and combined the results in a meta-analysis. This new study design yielded increased statistical power, leading to the discovery of six new EOC susceptibility loci. Variants at 1p36 (nearest gene *WNT4*), 4q26 (*SYNPO2*), 9q34.2 (*ABO*) and 17q11.2 (*ATAD5*) were associated with EOC risk, and at 1p34.3 (*RSPO1*) and 6p22.1 (*GPX6*) specifically with the serous EOC subtype, at $p<5x10^{-8}$. Incorporating these variants into risk assessment tools will improve clinical risk predictions for *BRCA1/2* mutation carriers.

The risk of developing invasive EOC is higher than the population average for relatives of women diagnosed with the disease[1,2], indicating the importance of genetic factors in disease susceptibility. Approximately 25% of the familial aggregation of EOC is explained by rare, high-penetrance alleles of *BRCA1* and *BRCA2* [3]. Furthermore, population-based GWAS have identified common variants associated with invasive EOC at 11 loci [4-9] but only six have also been evaluated in *BRCA1* and/or *BRCA2* mutation carriers. All loci displayed associations in mutation carriers that were consistent with the associations observed in the general population[10-12]. In addition, the 4q32.3 locus is associated with EOC risk for *BRCA1* mutation carriers only[13]. However, the common genetic variants explain less than 3.1% of the excess familial risk of EOC so additional susceptibility loci are likely to exist.

Women diagnosed with EOC and unaffected women from the general population ascertained through the Ovarian Cancer Association Consortium (OCAC)[14] and *BRCA1* and *BRCA2* mutation carriers from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA)[15] were genotyped as part of the Collaborative Oncological Gene-environment Study (COGS) using the iCOGS custom array. In addition, data were available for cases and controls from three EOC GWAS. We first evaluated whether the EOC susceptibility loci at 8q21.13, 10p12.31, 17q12, 5p15.33, and 17q21.31 recently identified by OCAC [7-9] also show evidence of association in *BRCA1* and *BRCA2* mutation carriers. Using data from >200,000 genotyped SNPs [7,13,16], we performed imputation of common variants from the 1000 Genomes Project data[17] and evaluated the associations of these SNPs with invasive EOC risk in OCAC and in *BRCA1* and *BRCA2* mutation carriers from CIMBA. Given the strong evidence for a significant overlap in loci predisposing to EOC in the general population and those associated with risk in *BRCA1* and *BRCA2* mutation carriers, we carried out a meta-analysis of the EOC risk associations in order to identify novel EOC susceptibility loci.

Genotype data were available for imputation on 15,252 *BRCA1* mutation carriers and 8,211 *BRCA2* mutation carriers, of whom 2,462 and 631, respectively, were affected with EOC[13,16]. From OCAC, genotyping data were available from 15,437 women with invasive EOC (including 9,627 with serous EOC) and 30,845 controls from the general population[7]. Imputation was performed separately for *BRCA1* carriers, *BRCA2* carriers, OCAC-COGS samples and the three OCAC GWAS (**Supplementary Tables 1-2; Supplementary Fig. 1; Supplementary Fig. 2**). The meta-analysis was based on 11,403,952 SNPs (**Supplementary Fig. 3)**.

Of five EOC susceptibility loci that have not yet been evaluated in mutation carriers, two were associated with EOC risk for both *BRCA1* and *BRCA2* mutation carriers at p<0.05 (10p12.31 and 17q21.31) (**Supplementary Table 3**). Overall, seven of the twelve known EOC susceptibility loci provided evidence of association in *BRCA1* mutation carriers and six were associated in *BRCA2* mutation carriers. However, with the exception of 5p15.33 (*TERT*), all loci had hazard ratio (HR) estimates in *BRCA1* and *BRCA2* carriers that were in the same direction as the odds ratio (OR) estimates for serous subtype EOC from OCAC (**Fig. 1**). Analysing the associations jointly in *BRCA1* and *BRCA2* carriers and serous EOC in OCAC provided stronger evidence of association, with smaller p-values for eight of the susceptibility variants compared to the analysis in OCAC alone.

Using the imputed genotypes, we observed no novel associations at $p<5x10^{-8}$ in the analysis of associations in *BRCA1* or *BRCA2* mutation carriers separately. However, we identified seven previously unreported associations (p-values$<5x10^{-8}$) in either OCAC alone, the meta-analysis of EOC associations in *BRCA1*, *BRCA2* carriers and OCAC, or in the meta-analysis in *BRCA1* and *BRCA2* carriers and serous EOC in OCAC (**Supplementary Fig. 4; Supplementary Tables 4-5**). SNPs in six of these loci remained genome-wide statistically significant after re-imputing genotypes with imputation parameters set to maximise accuracy (**Table 1; Fig. 1**). SNPs at 17q11.2 (near *ATAD5*) were found to be associated with invasive EOC in OCAC ($p<5x10^{-8}$) (**Table 1**). For the lead SNP, chr17:29181220:I, the estimated HR estimate for *BRCA1* mutation carriers was significantly different from the estimate in OCAC (p=0.005); the association for *BRCA2* carriers was consistent with the OCAC OR estimate (*BRCA2-OCAC* meta-analysis $p=2.6x10^{-9}$). SNPs at four loci were associated at $p<5x10^{-8}$ with risk of all invasive EOC in the meta-analysis (**Supplementary Fig. 5**): 1p36, 1p34.3, 4q26, and 9q34.2. At 1p34.3, the most strongly associated SNP, rs58722170, displayed stronger associations in the meta-analysis of serous EOC for OCAC ($p=2.7x10^{-12}$). In addition, SNPs at 6p22.1 were associated at genome-wide significance level in the meta-analysis of associations with serous EOC ($p=3.0x10^{-8}$), but not in the meta-analysis of all invasive EOC associations ($p=6.8x10^{-6}$).

The most significantly associated SNP at each of the six novel loci had high imputation accuracy ($r^2\geq0.83$). At the 1p34.3, 1p36, and 6p22.1 loci, there was at least one genome-wide significant genotyped SNP correlated with the lead SNP (pairwise $r^2\geq0.73$) (**Supplementary Table 6; Supplementary Fig. 5; Supplementary Note**). We genotyped the leading (imputed) SNPs of the three other loci in a subset of the samples using iPLEX (**Supplementary Note**). The correlations between the expected allele dosages from the imputation and the observed genotypes for the variants at 4q26 and 9q34.2, ($r^2=0.90$ and $r^2=0.84$, respectively) were consistent with the estimated imputation accuracy (0.93 and 0.83 for CIMBA samples). The lead SNP at 17q11.2 failed iPLEX design. However, the risk allele is highly correlated with the *AA* haplotype of two genotyped variants on the iCOGS array (rs9910051 and rs3764419). This haplotype is strongly associated with ovarian cancer risk in the subset of samples genotyped using iCOGS (*BRCA2-OCAC* meta-analysis $p=8.6x10^{-8}$ for haplotype, and $p=1.8x10^{-8}$ for chr17:29181220:I) (**Supplementary Table 7**).

None of the regions contained additional SNPs that displayed EOC associations at $p<10^{-4}$ in OCAC, *BRCA1* carriers or *BRCA2* carriers in multi-variable analyses adjusted for the lead SNP in each region, indicating that they each contain only one independent set of correlated highly associated variants (iCHAV). Relative to the 1000 Genomes Project data, we had genotyped or imputed data covering 91% of the genetic variation at 1p36, 84% at 1p34.3 and 83% at 4q26. The other three novel loci had coverage of less than 80% (**Supplementary Note**). There was evidence for heterogeneity at p<0.05 in

the associations with histological subtype in OCAC for the lead SNPs at 1p34.4 and 6p22.1, but not for at 1p36, 4q26, 9q34.2 and 17q11.2 (**Table 2**).

We carried out a competing risks association analysis in *BRCA1* and *BRCA2* mutation carriers in order to investigate whether these loci are also associated with breast cancer risk for mutation carriers (**Supplementary Note**). We used the most strongly associated genotyped SNPs for this purpose because the statistical method requires actual genotypes[18]. The EOC HR estimates were consistent with the estimates from the main analysis for all SNPs (**Supplementary Table 8**). None of the SNPs displayed associations with breast cancer risk at $p<0.05$.

At each of the six loci, we identified a set of SNPs with odds of less than 100 to 1 against being the causal variant; most are in non-coding DNA regions (**Supplementary Table 9**). None were predicted to have likely deleterious functional effects although some lie in or near chromatin biofeatures in fallopian tube and ovarian epithelial cells which may represent the functional regulatory targets of the risk SNPs (**Table 3; Supplementary Table 10**). We also evaluated the protein coding genes in each region for their role in EOC development, and as candidate susceptibility gene targets. Molecular profiling data from 496 HGSOCs performed by The Cancer Genome Atlas (TCGA) indicated frequent loss/deletion at four risk loci (1p36, 4q26, 9q34.2 and 17q11.2) (**Supplementary Table 11**). Consistent with this, *WNT4* and *ABO* were significantly down-regulated in ovarian tumours while *ATAD5* was up-regulated. Somatic coding sequence mutations in the six genes nearest the index SNPs were rare. We performed expression quantitative trait locus (eQTL) analysis in a series of 59 normal ovarian tissues (**Supplementary Table 12**) to evaluate the gene nearest the top ranked SNP at each locus. For the five genes expressed in normal cells, we found no statistically significant eQTL associations for any of the putative causal SNPs at each locus; neither did we find any significant tumour-eQTL associations for these genes based on data from TCGA (**Supplementary Table 12**). At the 1p36 locus, the most strongly associated variant, rs56318008, is located in the promoter region of *WNT4* which encodes a ligand in the WNT signal transduction pathway, critical for cell proliferation and differentiation. Using a luciferase reporter assay we found no effect of these putatively causal SNPs on *WNT4* transcription in iOSE4 normal ovarian cells (**Fig. 2**). Some of the putative causal SNPs at 1p36 are located in *CDC42* and *LINC00339,* and several are in putative regulatory domains in ovarian tissues (**Supplementary Table 10**; **Fig. 2**). *CDC42* is known to play a role in migration and signalling in ovarian and breast cancer[19,20]. SNPs at 1p36 are also associated with increased risk of endometriosis and *WNT4*, *CDC42* and *LINC00339* have all been implicated in endometriosis[21], a known risk factor for endometrioid and clear cell EOC[22].

The strongest associated variant at 1q34, rs58722170, is located in *RSPO1*, which encodes R-spondin 1, a protein involved in cell proliferation (**Supplementary Fig. 6**). RSPO1 is important in tumorigenesis and early ovarian development[23,24], and regulates *WNT4* expression in the ovaries [25]. *SYNPO2* at 4q26 encodes myopodin which is involved in cell motility and growth[26] and has a reported tumour suppressor role[27-30]. rs635634 is located upstream of the *ABO* gene (**Supplementary Fig. 7**). A moderately correlated variant (rs505922, $r^2=0.52$) determines ABO blood group and is associated with increased risk of pancreatic cancer[31,32]. Previous studies in OCAC also showed a modestly increased risk of EOC for individuals with the A blood group[33]. The moderate correlation between rs635634 and rs505922 and considerably weaker EOC association of rs505922 ($p=1.2\times10^{-5}$) suggests that the association with blood group is probably not driving the association with risk. The indel, 17:29181220:I, at 17q11.2 is located in *ATAD5* which acts as a tumour

suppressor gene[34-36] (**Supplementary Fig. 8**). ATAD5 modulates the interaction between RAD9A and BCL2 in order to induce DNA damage related apoptosis. Finally, rs116133110, at 6p22.1, lies in *GPX6* which has no known role in cancer.

The six novel loci reported in this study increase the number of genome-wide significant common variant loci so far identified for EOC to 18. Taken together, these explain approximately 3.9% of the excess familial relative risk of EOC in the general population, and account for approximately 5.2% of the EOC polygenic modifying variance in *BRCA1* mutation carriers and 9.3% in *BRCA2* mutation carriers. The similarity in the magnitude of associations between *BRCA1* and *BRCA2* carriers and population-based studies suggests a general model of susceptibility whereby *BRCA1* and *BRCA2* mutations and common alleles interact multiplicatively on the relative risk scale for EOC [37]. This model predicts large differences in absolute EOC risk between individuals carrying many alleles and individuals carrying few risk alleles of EOC susceptibility loci for *BRCA1* and *BRCA2* mutation carriers [13,16]. Incorporating EOC susceptibility variants into risk assessment tools will improve risk prediction and may be particularly useful for *BRCA1* and *BRCA2* mutation carriers.

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Institute and National Human Genome Research Institute (dbGap accession number phs000178.v8.p7). A full list of the investigators who contributed to the generation of the data is available on the website (see URL). The cBio portal was developed and is maintained by the Computational Biology Center at Memorial Sloan-Kettering Cancer Center.

Figure legends

Figure 1. Hazard ratios for the association with EOC of 12 previously reported epithelial ovarian cancer susceptibility variants and the six novel susceptibility variants for OCAC, *BRCA1* mutation carriers and *BRCA2* mutation carriers

Figure 2. The 1p36 epithelial ovarian cancer susceptibility locus

A) The Manhattan plot depicts the strength of association between all imputed and genotyped SNPs across the region bound by hg19 co-ordinates chr1:21922893-22991643. The dotted line represents the genome-wide significance level $5x10^{-8}$. Additional tracks show genes and enhancers in ovary as described in Hnisz et al[38]. Positions of SNPs for which imputation $r^2<0.3$ and/or minor allele frequency <0.005 are shown in the bottom track as 'untyped' SNPs.

B) The shaded iCHAV from (A) is shown depicting the genes and the location of the *WNT4* promoter construct as a red box. Red ticks show the positions of the putative causal variants following likelihood ratio testing. Signals from FAIRE-seq data derived from ovarian cells are represented by black marks, and the locations of predicted *CDC42* enhancers[38] as blue boxes. The positions of genotyped SNPs, and those that were neither genotyped nor well imputed ('untyped'), are shown.

C) Normalised luciferase reporter activity following triplicate transfections of wildtype and risk haplotype *WNT4* promoter constructs in iOSE4 cells. Error bars represent standard error from three independent experiments.

Author Contributions

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Table 1. Association test results for loci associated at $p<5x10^{-8}$ in the second imputation stage. Results reported for ovarian cancer in *BRCA1* and *BRCA2* mutation carriers, ovarian cancer as well as serous subtype in OCAC, the meta-analysis for ovarian cancer, and for the meta-analysis for all tumour histologies in *BRCA1* and *BRCA2* and serous ovarian cancer in OCAC. SNP with smallest p-value reported for each locus

						OCAC all histologies			**OCAC serous**		***BRCA1* carriers**			***BRCA2* carriers**			**MA all histologies[1]**	**MA serous[2]**
Locn	**Nearest gene**	**rs#**	**Ref[6]**	**Eff[6]**	**EAF[7]**	**r^2***	**OR (95%CI)**	**P**	**OR (95%CI)**	**P**	**r^2***	**HR (95%CI)**	**P**	**r^2***	**HR (95%CI)**	**P**	**P**	**P**
1p36	*WNT4*	rs56318008	C	T	0.15	0.98	1.11 (1.07-1.16)	$3.9x10^{-7}$	1.12 (1.07-1.18)	**$3.1x10^{-6}$**	0.98	1.15 (1.05-1.26)	$3.1x10^{-3}$	0.98	1.03 (0.86-1.23)	0.74	$7.6x10^{-9}$	$5.7x10^{-8}$
1p34.3	*RSPO1*	rs58722170	G	C	0.23	0.85	1.08 (1.04-1.12)	$9.7x10^{-5}$	1.12 (1.08-1.18)	$1.1x10^{-7}$	0.83	1.14 (1.05-1.23)	$1.5x10^{-3}$	0.83	1.35 (1.17-1.57)	$5.2x10^{-5}$	$1.6 x10^{-8}$	$2.7 x10^{-12}$
4q26	*SYNPO2*	rs17329882	A	C	0.24	0.95	1.09 (1.06-1.13)	$5.9x10^{-7}$	1.11 (1.07-1.16)	$6.4x10^{-7}$	0.93	1.08 (1.00-1.17)	0.042	0.93	1.15 (1.00-1.33)	0.06	$1.4 x10^{-8}$	$1.6 x10^{-8}$
6p22.1	*GPX6*	rs116133110[4]	T	C	0.31	0.99	0.93 (0.91-0.97)	$9.0x10^{-5}$	0.91 (0.87-0.94)	$2.6 x10^{-7}$	0.99	0.92 (0.86-0.99)	0.023	0.99	0.97 (0.85-1.10)	0.64	$6.8x10^{-6}$	$3.0 x10^{-8}$
9q34.2	*ABO*	rs635634	C	T	0.19	0.85	1.11 (1.07-1.16)	$1.1x10^{-7}$	1.12 (1.08-1.18)	$1.0x10^{-6}$	0.83	1.11 (1.02-1.21)	0.012	0.83	1.05 (0.89-1.23)	0.55	$4.4 x10^{-9}$	$4.2 x10^{-8}$
17q11.2	*ATAD5*	chr17:29181220:I[5]	A	AT	0.28	0.95	0.91 (0.88-0.94)	$5.4x10^{-9}$	0.91 (0.87-0.94)	$8.1x10^{-7}$	0.94	1.01 (0.94-1.08)	0.88	0.93	0.92 (0.80-1.05)	0.23	$2.6 x10^{-9}$*[3]	$3.9 x10^{-7}$*[3]

* Imputation accuracy r^2 estimate

[1] P-value from the meta-analysis association test for ovarian cancer in OCAC and *BRCA1* and *BRCA2* carriers

[2] P-value from the meta-analysis association test for ovarian cancer in *BRCA1* and *BRCA2* carriers and serous ovarian cancer in OCAC

*[3] meta-analysis of ovarian cancer associations in *BRCA2* carriers and OCAC only

[4] rs116133110 listed as rs6456822 on dbSNP

[5] chr17:29181220:I listed as rs199661266 on dbSNP

[6] Reference and effect allele

[7] Effect allele frequency

Table 2. Associations with ovarian cancer subtypes in OCAC samples for loci associated with ovarian cancer at $p<5x10^{-8}$ in the meta-analysis

		All histologies		Serous		Endometrioid		Clear cell		Mucinous		
Locus	**rs#**	**OR (95%CI)**	**P**	**OR (95%CI)**	**P**	**OR (95%CI)**	**P**	**OR (95%CI)**	**P**	**OR (95%CI)**	**P**	**p-het***
1p36	rs56318008	1.11 (1.06-1.15)	$8x10^{-7}$	1.12 (1.06-1.17)	$6x10^{-6}$	1.09 (1.00-1.19)	0.05	1.24 (1.10-1.39	$5x10^{-4}$	1.03 (0.91-1.17)	0.65	0.22
1p34.3	rs58722170	1.07 (1.03-1.11)	$2x10^{-4}$	1.12 (1.07-1.17)	$4x10^{-7}$	0.94 (0.87-1.02)	0.16	1.00 (0.89-1.12)	0.98	1.08 (0.97-1.21)	0.17	0.001
4q26	rs17329882	1.09 (1.06-1.13)	$3x10^{-7}$	1.11 (1.07-1.16)	$3x10^{-7}$	1.09 (1.01-1.18)	0.020	1.06 (0.96-1.18)	0.26	1.11 (0.99-1.23)	0.06	0.88
6p22.1	rs116133110	0.94 (0.91-0.97)	$9x10^{-5}$	0.91 (0.87-0.94)	$3x10^{-7}$	0.95 (0.89-1.02)	0.16	1.05 (0.95-1.15)	0.34	1.03 (0.94-1.14)	0.53	0.008
9q34.2	rs635634	1.12 (1.08-1.16)	$9x10^{-9}$	1.13 (1.08-1.18)	$2x10^{-7}$	1.12 (1.03-1.21)	0.007	1.03 (0.92-1.16)	0.58	1.23 (1.10-1.38)	$3x10^{-4}$	0.23
17q11.2	chr17:29181 220:I	0.90 (0.87-0.93)	$1x10^{-9}$	0.90 (0.87-0.94)	$2x10^{-7}$	0.88 (0.82-0.95)	$5x10^{-4}$	0.88 (0.80-0.98)	0.020	1.01 (0.91-1.12)	0.84	0.18

* p-value for the heterogeneity in associations with different tumour subtypes

Table 3: Summary of data on SNPs, closest gene and all genes in 1 MB region for each locus

Loci	Position of top SNP	# putatively causal SNPs	Genes in window of putatively causal SNPs	# SNPs aligned w/ biofeatures [b]	Normal eQTL closest gene	Tumour DNA copy number	Significant expression difference in tumour vs normal	Known role of gene in cancer	# Genes in 1MB region	Other known cancer genes in 1MB region
1p36	promoter region of *WNT4*	39	*WNT4, CDC42, LINC00339*	11	NS	loss		Yes	11	*RAP1GAP, CDC42*
1p34.3	intron 3 of *RSPO1*	15	*RSPO1*	0	NS	gain		Yes	22	*C1orf109, FHL3*
4q26	intron 3 of *SYNPO2*	4	*SYNPO2*	2	NS**	loss	down	Yes	12	none
6p22.1	intron 1 of *GPX6*	22	*GPX6, GPX5*	1	N/A	gain			23	*ZKSCAN3, TRIM27*
9q34.2	4.3kb upstream of *ABO*	18	*ABO, SLC2A6**	1	NS	loss	down	Yes	32	*TSC1, RALGDS, RPL7A, VAV2*
17q11.2	intron 6 of *ATAD5*	16	*ATAD5, TEFM, ADAP2, CRLF3, SUZ12P1*	0	NS	loss	up	Yes	17	*NF1*

Proximal promoter regions were defined as 1kb upstream of the transcription start site

N/A indicated no expression of *GPX6* in normal tissues. NS, not significant.

[b] Biofeatures defined as open chromatin, H3K4me3 or H3K27ac marks detected in normal ovarian and/or fallopian cells

* There are 16 genes in this region; *ABO, SURF6, MED22, RPL7A, SNORD24, SNORD36B, SNORD36A, SNORD36C, SURF1, SURF2, SURF4, C9orf96, REXO4, ADAMTS13, CACFD1, SLC2A6,* however all SNPs are within or upstream of *ABO* or upstream of *SLC2A6*.

** Trend p=0.067

METHODS

Study populations

We obtained data on *BRCA1* and *BRCA2* mutation carriers through CIMBA. Eligibility in CIMBA is restricted to females 18 years or older with pathogenic mutations in *BRCA1* or *BRCA2*. The majority of the participants were sampled through cancer genetics clinics[15], including some related participants. Fifty-four studies from 27 countries contributed data. After quality control, data were available on 15,252 *BRCA1* mutation carriers and 8,211 *BRCA2* mutation carriers, of whom 2,462 and 631, respectively, were affected with EOC (**Supplementary Table 1**).

Data were available for the stage 1 of three population-based EOC GWAS. These included 2,165 cases and 2,564 controls from a GWAS from North America ("US GWAS")[39], 1,762 cases and 6,118 controls from a UK-based GWAS ("UK GWAS")[6], and 441 cases and 441 controls from the Mayo GWAS. Furthermore, 11,069 cases and 21,722 controls were genotyped using the iCOGS array ("OCAC-iCOGS" stage data). Overall, 43 studies from 11 countries provided data on 15,347 women diagnosed with invasive epithelial EOC, 9,627 of whom were diagnosed with serous EOC, and 30,845 controls from the general population.

All subjects included in this analysis were of European descent and provided written informed consent as well as data and blood samples under ethically approved protocols. Further details of the OCAC and CIMBA study populations as well as the genotyping, quality control and statistical analyses have been described elsewhere[7,13,16].

Genotype data

Genotyping and imputation details for each study are shown in **Supplementary Table 1**.

Confirmatory genotyping of imputed SNPs

To evaluate the accuracy of the imputation of the SNPs we found to be associated with EOC risk, we genotyped rs17329882 (4q26) and rs635634 (9q34.2) in a subset of 3,541 subjects from CIMBA using Sequenon's iPLEX technology. The lead SNP at 17q11.2, chr17:29181220:I failed iPLEX design. We performed quality control of the iPLEX data according to the CIMBA guidelines. After quality control, we used the imputation results to generate the expected allele dosage for each genotyped sample and computed the Pearson product-moment correlation coefficient between the expected allele dosage and the observed genotype. The squared correlation coefficient was compared to the imputation accuracy as estimated from the imputation.

Quality control of GWAS and iCOGS genotyping data

We carried out quality control separately for *BRCA1* carriers, *BRCA2* carriers, the three OCAC GWAS, and OCAC-iCOGS samples, but quality criteria were mostly consistent across studies. We excluded samples if they were not of European ancestry, if they had a genotyping call rate < 95%, low or high heterozygosity, if they were not female or had ambiguous sex, or were duplicates (cryptic or intended). In OCAC studies, one individual was excluded from each pair of samples found to be first-degree relatives and duplicate samples between the iCOGS stage and any of the GWAS were excluded from the iCOGS data. SNPs were excluded if they were monomorphic, had call rate<95%,

showed evidence of deviation from Hardy-Weinberg equilibrium or had low concordance between duplicate pairs. For the Mayo GWAS and the UK GWAS, we also excluded rare SNPs (MAF<1% or allele count <5, respectively). We visually inspected genotype cluster plots for all SNPs with $P<10^{-5}$ from each of the newly identified loci. We used the R GenABEL library version 1.6.7 for quality control [40].

Genotype data were available for analysis from iCOGS for 199,526 SNPs in OCAC-iCOGS, 200,720 SNPs in *BRCA1* mutation carriers, and 200,908 SNPs in *BRCA2* mutation carriers. After QC, for the GWAS, data were available on 492,956 SNPs for the US GWAS, 543,529 SNPs for the UK GWAS and 1,587,051 SNPs for the Mayo GWAS (**Supplementary Table 2**).

Imputation

We performed imputation separately for *BRCA1* carriers, *BRCA2* carriers, OCAC-iCOGS samples and each of the OCAC GWAS. We imputed variants from the 1000 Genomes Project data using the v3 April 2012 release[17] as the reference panel. For OCAC-iCOGS, the UK GWAS and the Mayo GWAS, imputation was based on the 1000 Genomes Project data with singleton sites removed. To improve computation efficiency we initially used a two-step procedure, which involved pre-phasing in the first step and imputation of the phased data in the second. We carried out pre-phasing using the SHAPEIT software[41]. We used the IMPUTE version 2 software for the subsequent imputation[42] for all studies with the exception of the US GWAS for which the MACH algorithm implemented in the minimac software version 2012.8.15, mach version 1.0.18 was used. To perform the imputation we divided the data into segments of approximately 5Mb each. We excluded SNPs from the association analysis if their imputation accuracy was $r^2<0.3$ or their minor allele frequency (MAF) was <0.005 in *BRCA1* or *BRCA2* carriers or if their accuracy was $r^2<0.25$ in OCAC-iCOGS, the UK GWAS, UK GWAS or Mayo GWAS.

We performed more accurate imputation for the regions around the novel EOC loci from the joint analysis of the data from *BRCA1* and *BRCA2* carriers and the general population (any SNP with $P<5x10^{-8}$). The boundaries of these regions were set +/-500kb from any significantly associated SNP in the region. As in the first run, the 1000 Genomes Project data v3 were used as the reference panel and the software IMPUTE2 was applied. However, for the second round of imputation, we imputed genotypes without pre-phasing in order to improve accuracy. To further increase the imputation accuracy we changed some of the default parameters in the imputation procedure. These included an increase of the MCMC iterations to 90 (out of which the first 15 were used as burn-in), an increase of the buffer region to 500kb and an increase of the number of haplotypes used as templates when phasing observed genotypes to 100. These changes were applied consistently for all data sets.

Statistical analyses

Association analyses in the unselected ovarian cancer cases and controls from OCAC

We evaluated the association between genotype and disease using logistic regression by estimating the associations with each additional copy of the minor allele (log-additive models). The analysis was adjusted for study and for population substructure by including the eigenvectors of the first five ancestry specific principal components as covariates in the model. We used the same approach to

evaluate the SNP associations with serous ovarian cancer after excluding all cases with any other or with unknown tumour subtype. For imputed SNPs we used expected dosages in the logistic regression model to estimate SNP effect sizes and p-values. We carried out analyses separately for OCAC-iCOGS and the three GWAS and pooled thereafter using a fixed effects meta-analysis. We carried out the analysis of re-imputed genotypes of putative novel susceptibility loci jointly for the OCAC-iCOGS and GWAS samples. All results are based on the combined data from iCOGS and the three GWAS. We used custom written software for the analysis.

Associations in BRCA1 and BRCA2 mutation carriers from CIMBA

We carried out the ovarian cancer association analyses separately for *BRCA1* and *BRCA2* mutation carriers. The primary analysis was carried out within a survival analysis framework with time to ovarian cancer diagnosis as the endpoint. Mutation carriers were followed until the age of ovarian cancer diagnosis, or risk-reducing salpingo-oophorectomy (RRSO) or age at last observation. Breast cancer diagnosis was not considered as a censoring event. In order to account for the non-random sampling of *BRCA1* and *BRCA2* mutation carriers with respect to their disease status we conducted the analyses by modelling the retrospective likelihood of the observed genotypes conditional on the disease phenotype [18]. We assessed the associations between genotype and risk of ovarian cancer using the 1 degree of freedom score test statistic based on the retrospective likelihood [18,43]. To account for the non-independence among related individuals in the sample, we used an adjusted version of the score test statistic, which uses a kinship adjusted variance of the score [44]. We evaluated associations between imputed genotypes and ovarian cancer risk using a version of the score test as described above but with the posterior genotype probabilities replacing the genotypes. All analyses were stratified by the country of origin of the samples.

We carried out the retrospective likelihood analyses in CIMBA using custom written functions in Fortran and Python. The score test statistic was implemented in R version 3.0.1 [45].

We evaluated whether there is evidence for multiple independent association signals in the region around each newly identified locus by evaluating the associations of genetic variants in the region while adjusting for the SNP with the smallest meta-analysis p-value in the respective region. This was done separately for *BRCA1* carriers, *BRCA2* carriers and OCAC.

For one of the novel associations, it was not possible to confirm the imputation accuracy of the lead SNP chr17:29181220:I at 17q11.2 through genotyping. Therefore, we inferred two-allele haplotypes for rs9910051 and rs3764419, highly correlated with the lead SNP (r^2=0.95), using an in-house program. These variants were genotyped on the iCOGS array and therefore this analysis was restricted to 14,733 ovarian cancer cases and 9,165 controls from OCAC-COGS, and 8,185 *BRCA2* mutation carriers that had available genotypes for both variants based on iCOGS. The association between the AA haplotype and risk was tested using logistic regression in OCAC and using Cox regression in *BRCA2* mutation carriers.

Meta-analysis

We conducted a meta-analysis of the EOC associations in *BRCA1*, *BRCA2* carriers and the general population for genotyped and imputed SNPs using an inverse variance approach assuming fixed effects. We combined the logarithm of the per-allele hazard ratio estimate for the association with

EOC risk in *BRCA1* and *BRCA2* mutation carriers and the logarithm of the per-allele odds ratio estimate for the association with disease status in OCAC. For the associations in *BRCA1* and *BRCA2* carriers, we used the kinship adjusted variance estimator[44] which allows for inclusion of related individuals in the analysis. We only used SNPs with results in OCAC and in at least one of the *BRCA1* or the *BRCA2* analyses. We carried out two separate meta-analyses, one for the associations with EOC in *BRCA1* carriers, *BRCA2* carriers and EOC in OCAC, irrespective of tumour histological subtype, and a second using only the associations with serous EOC in OCAC. The number of *BRCA1* and *BRCA2* samples with tumour histology information was too small to allow for subgroup analyses. However, previous studies have demonstrated that the majority of EOCs in *BRCA1* and *BRCA2* mutation carriers are high-grade serous[49-53]. Meta-analyses were carried out using the software "metal", 2011-03-25 release[54].

Candidate causal SNPs in each susceptibility region

In order to identify a set of potentially causal variants we excluded SNPs with a likelihood of being causal of less than 1:100, by comparing the likelihood of each SNP from the association analysis with the one of the most strongly associated SNP [46]. The remaining variants were then analysed using pupasuite 3.1 to identify potentially functional variants (**Supplementary Table 9**).

Functional analysis

Expression quantitative trait locus (eQTL) analysis in normal OSE and FTSE cells

Early-passage primary normal ovarian surface epithelial cells (OSECs) and fallopian tube epithelial cells were harvested from disease-free ovaries and fallopian tubes. Normal ovarian epithelial cells were collected by brushing the surface of the ovary with a sterile cytobrush, and were cultured in NOSE-CM [55]. Fallopian tube epithelial cells were harvested by Pronase digestion as previously described [56], plated onto collagen-coated plastics (Sigma) and cultured in DMEM/F12 (Sigma-Aldrich) supplemented with 2% Ultroser G (BioSepra) and 1X penicillin/streptomycin (Lonza). By the time of RNA harvesting, fallopian tube cultures tested consisted of PAX8 positive fallopian tube secretory epithelial cells (FTSECs), consistent with previous observations that ciliated epithelial cells from the fallopian tube do not proliferate *in vitro*.

For gene expression analysis, RNA was harvested from 59 early passage samples: 54 OSECs and 5 FTSECs from cell cultures harvested at ~80% confluency using the QIAgen miRNAeasy kit with on-column DNase 1 digestion. 500ng RNA was reverse transcribed using the Superscript III kit (Life Technologies). We preamplified 10ng cDNA using the TaqMan® Preamp Mastermix; the resulting product was diluted 1:60 and used to quantify gene expression using the following TaqMan® gene expression probes: WNT4, Hs01573504_m1; RSPO1, Hs00543475_m1; SYNPO2, Hs00326493_m1; ATAD5, Hs00227495_m1 and GPX6, Hs00699698_m1. Four control genes were also included: ACTB, Hs00357333_g1; GAPDH, Hs02758991_g1; HMBS, Hs00609293_g1 and HPRT1 Hs02800695_m1 (all Life Technologies). Assays were run on an ABI 7900HT Fast Real-Time PCR system (Life Technologies).

Data Analysis: Expression levels for each gene were normalized to the average of all four control genes. Relative expression levels were calculated using the δδCt method. Genotyping was performed on the iCOGs chips, as described above. Where genotyping data were not available for

the most risk-associated SNP, the next most significant SNP was used: rs3820282 at 1p36, rs12023270 at 1p34.3, rs752097 at 4q26, rs445870 at 6p22.1, rs505922 at 9q34.2 and rs3764419 at 17q11.2. Correlations between genotype and gene expression were calculated in 'R'. Genotype specific gene expression in the normal tissue cell lines (eQTL analysis) was compared using the Jonckheere-Terpstra test. IData were normalized to the four control genes and we tested for eQTL associations, grouping OSECs and FTSECs together. Secondly, OSECs were analysed alone. eQTL analyses were performed using 3 genotype groups, or two groups (with the rare homozygote samples grouped together with the heterozygote samples).

eQTL analysis in primary ovarian tumours:

eQTL analysis in primary tumours was based on the publicly available data available from The Cancer Genome Atlas (TCGA) project, which includes 489 primary high grade serous ovarian cancers. The methods have been described elsewhere[57]. Briefly, we determined the ancestry for each case based on the germ line genotype data using EIGENSTRAT software with 415 HapMap genotype profiles as a control set. Only populations of Northern and Western European ancestries were included. We first performed a *cis*-eQTL analyses using a method we described previously, in which the association between 906,600 germline genotypes and the expression levels of mRNA or miRNA (located within 500Kb on either side of the variant) were evaluated using linear regression model with the effects of somatic copy number and CpG methylation being deducted (For miRNA expression, the effect of CpG methylation is not adjusted for since the data are not available). To adjust for multiple tests, we adjusted the test P values using Benjamini-Hochberg method. A significant association was defined by a false discovery rate (FDR) of less than 0.1.

Having established a genome-wide *cis*-eQTL associaitions in this series of tumours, we then evaluated *cis*-eQTL associations for the top risk associations between each of the six new loci and the gene in closest proximity to the risk SNP. For each risk locus, we retrieved the genotype of all SNPs in ovarian cancer cases based on the Affymetrix 6.0 array. Using these genotypes and the impute2 March 2012 1000 Genomes Phase I integrated variant cosmopolitan reference panel of 1,092 individuals (Haplotypes were phased via SHAPEIT), we imputed the genotypes of SNPs in the 1000 Genomes Project in the target regions for TCGA samples[58]. For each risk locus where data for the most risk-associated variant were not available, we retrieved the imputed variants tightly correlated with the most risk-associated variant. We then tested for association between imputed SNPs and gene expression using the linear regression algorithm described above, where each imputed SNP was coded as an expected allele count. Again, significant associations are defined by a false discovery rate (FDR) of less than 0.1.

Regulatory profiling of normal ovarian cancer precursor tissues

We performed genome-wide formaldehyde assisted regulatory element (FAIRE) and ChIP seq with histone 3 lysine 27 acetylation (H3K27ac) and histone 3 lysine 4 monomethylation (H3K4me) for two normal OSECs, two normal FTSECs and two HGSOC cell lines (UWB1.289 and CAOV3) [Shen et al. in preparation]. These datasets annotate epigenetic signatures of open chromatin, and collectively indicate transcriptional enhancer regions. We analysed the FAIRE-seq and ChIP-seq datasets and publically available genomic data on promoter and UTR domains, intron/exon boundaries, and

positions of non-coding RNA transcripts to identify SNPs from the 100:1 likely causal set that align with biofeatures that may provide evidence of SNP functionality.

Candidate Gene Analysis Using Genome Wide Profiling of Primary Ovarian Cancers:

Data Sets: The Cancer Genome Atlas (TCGA) Project and COSMIC Datasets

TCGA has performed extensive genomic analysis of tumours from a large number of tissue types including almost 500 high-grade serous ovarian tumours. These data include somatic mutations, DNA copy number, mRNA and miRNA expression and DNA methylation. COSMIC is the catalogue of somatic mutations in cancer that collates information on mutations in tumours from the published literature[59]. They have also identified The Cancer Gene Census, which is a list of genes known to be involved in cancer. Data are available on a large number of tissue types, including 2,809 epithelial ovarian tumours.

Somatic coding sequence mutations: We analysed all genes for coding somatic sequence mutations generated from either whole exome or whole genome sequencing. In TCGA, whole exome sequencing data were available for 316 high-grade serous EOC cases. In addition, we determined whether mutations had been reported in COSMIC[59] and whether the gene was a known cancer gene in the Sanger Cancer Gene Census.

mRNA expression in tumour and normal tissue: Normalized and gene expression values (Level 3) gene expression profiling data were obtain from the TCGA data portal for three different platforms (Agilent, Affymetrix HuEx and Affymetrix U133A). We analysed only the 489 primary serous ovarian tumour samples included in the final clustering analysis [58] and eight normal fallopian tube samples. The boxplot function in R was used to compare ovarian tumour samples to the fallopian tube for 91 coding genes with expression data on any platform within a 1MB region around the most significant SNP at the six loci. A difference in relative expression between EOC and normal tissue was carried out using the Wilcoxon rank-sum test.

DNA copy number analysis: Serous EOC samples for 481 tumours with log2 copy number data were analysed using the cBio portal for analysis of TCGA data [60,61]. For each gene in a region the classes of copy number; homozygous deletion, heterozygous loss, diploid, gain, and amplification were queried individually using the advanced onco query language (OQL) option. The frequency of gain and amplification were combined as “gain”, and homozygous deletion and heterozygous loss were combined as “loss”.

Analysis of copy number vs mRNA expression: Serous EOC samples for 316 complete tumours (those with CNA, mRNA and sequencing data) were analysed. Graphs were generated using the cBio portal for analysis of TCGA data and the setting were mRNA expression data Z-score (all genes) with the Z-score threshold of 2 (default setting) and putative copy number alterations (GISTIC). The Z-score is the number of standard deviations away from the mean of expression in the reference population. GISTIC is an algorithm that attempts to identify significantly altered regions of amplification or deletion across sets of patients.

Luciferase Reporter Assay

The putative causal SNPs at the 1p36 locus lie in the *WNT4* promoter and so we tested their effect on transcription in a luciferase reporter assay (**Fig. 2D**). Wild-type and risk haplotype (comprising five correlated variants) sequences corresponding to the region bound by hg19 co-ordinates chr1:22469416-22470869 were generated by Custom Gene Synthesis (GenScript Corporation), and then sub-cloned into pGL3-basic (Promega). Equimolar amounts of luciferase constructs (800 ng) and pRL-TK Renilla (50 ng) were co-transfected into ~8 x 10^4 iOSE4[62] normal ovarian cells in triplicate wells of 24 well plates using LipoFectamine 2000 (Life Technologies). Independent transfections were repeated three times. The Dual-Glo Luciferase Assay kit (Promega) was used to assay luciferase activity 24 hours post transfection using a BioTek Synergy H4 plate reader. The iOSE-4 cell line (derived by K. Lawrenson) was maintained under standard conditions and routinely tested for *Mycoplasma* and short tandem repeat profiled.

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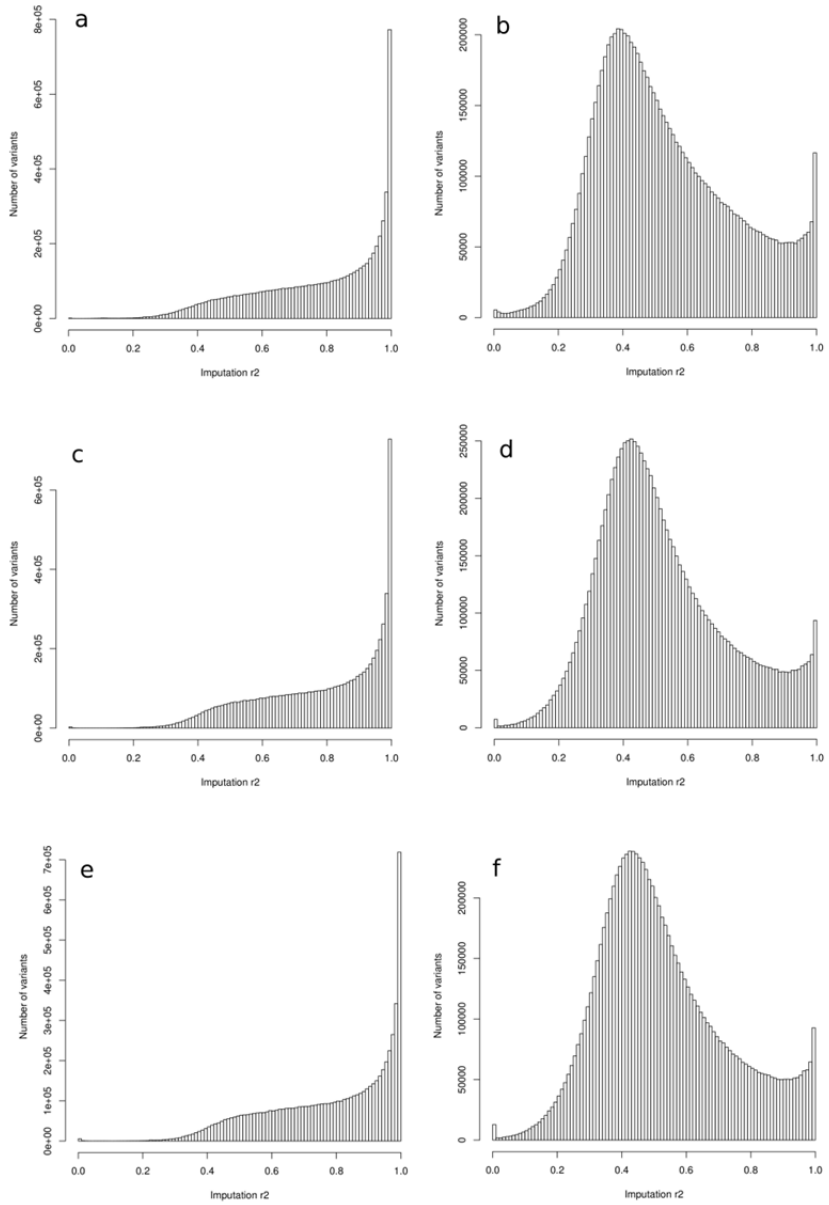
Identification of six new susceptibility loci for invasive epithelial ovarian cancer

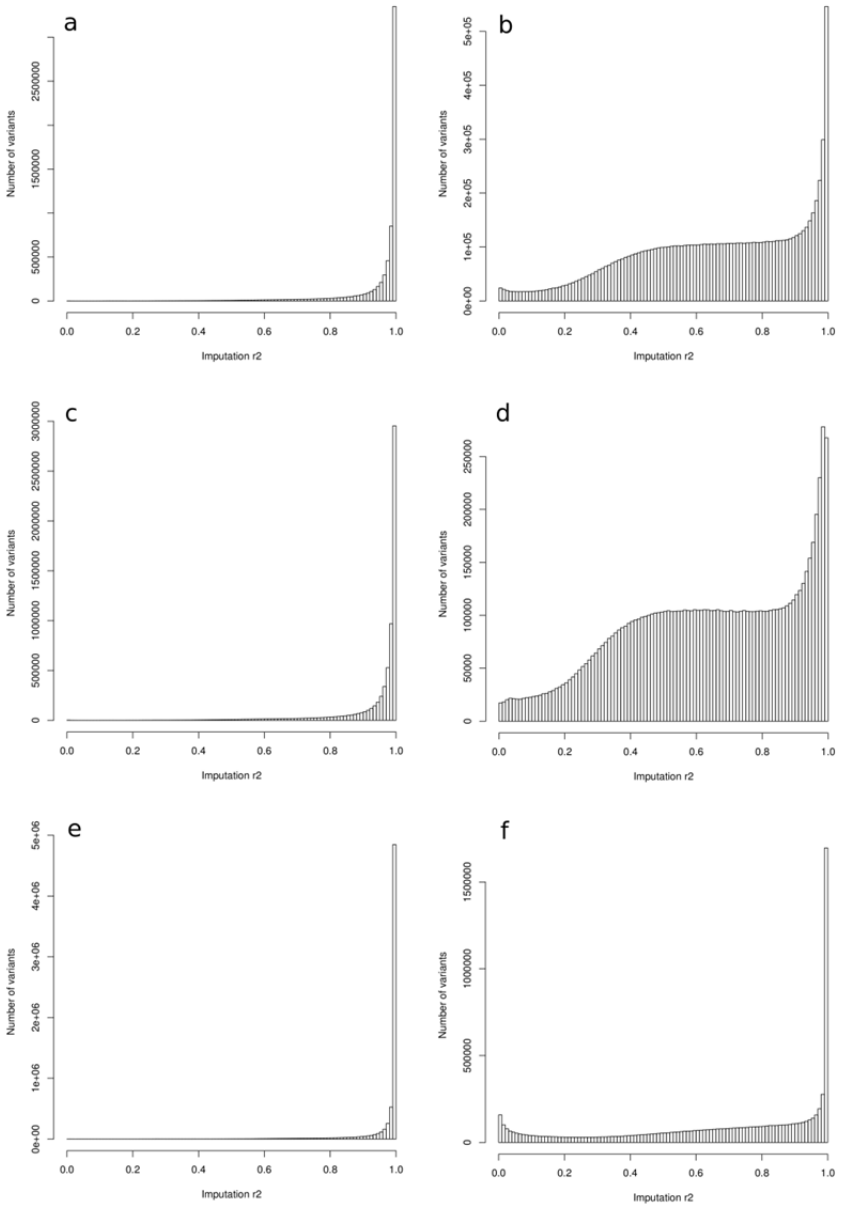
Supplementary Figures



Supplementary Figure 1

Imputation accuracy distribution.

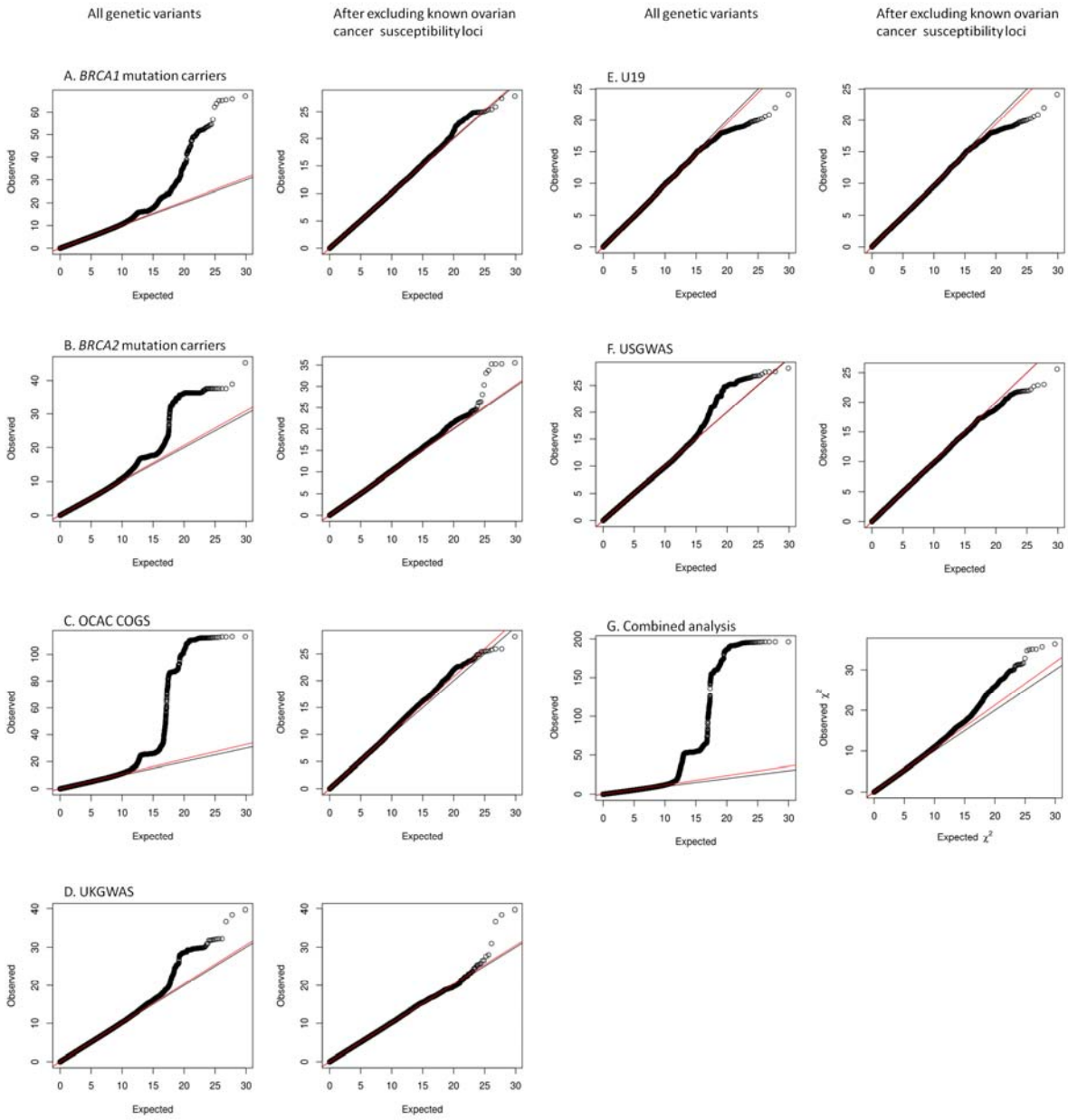
Histogram showing the distribution of imputation accuracy estimates r^2 in the first genotype imputation on the 1000 Genomes Project data v3 for SNPs with MAF >0.05 (a, c, e) and for SNPs with MAF ≤0.05 (b,d,f) in OCAC-iCOGS (a, b), *BRCA1* mutation carriers (c, d) and *BRCA2* mutation carriers (e, f).



Supplementary Figure 2

Imputation accuracy distribution.

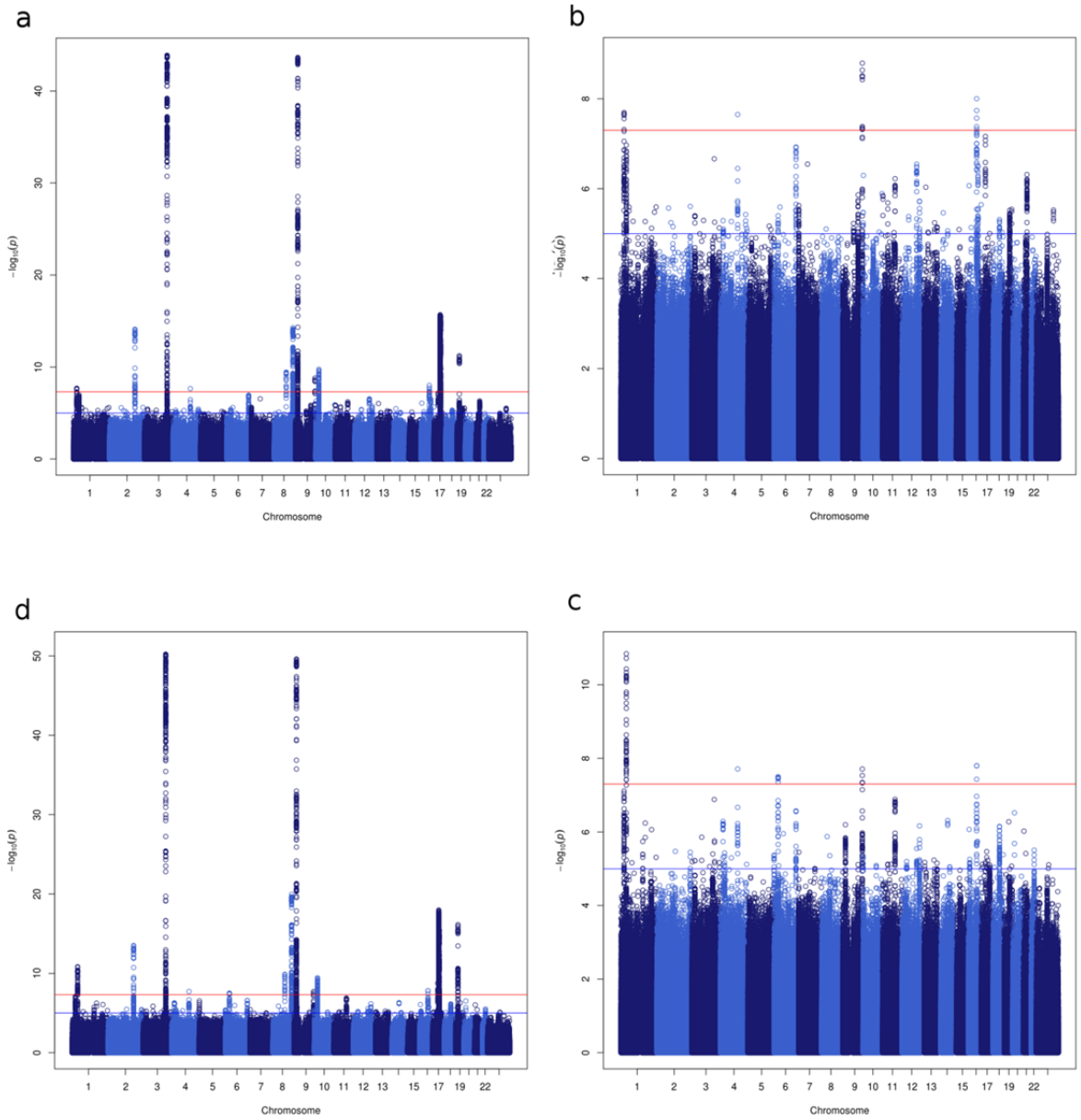
Histogram showing the distribution of imputation accuracy estimates r2 in the first genotype imputation on the 1000 Genomes Project data v3 for SNPs with MAF >0.05 (a, c, e) and for SNPs with MAF ≤0.05 (b,d,f) in the UK GWAS (a, b), the US GWAS (c, d) and the U19 GWAS (e, f).



Supplementary Figure 3

Quantile-quantile plot for genetic variants from the genotype imputation.

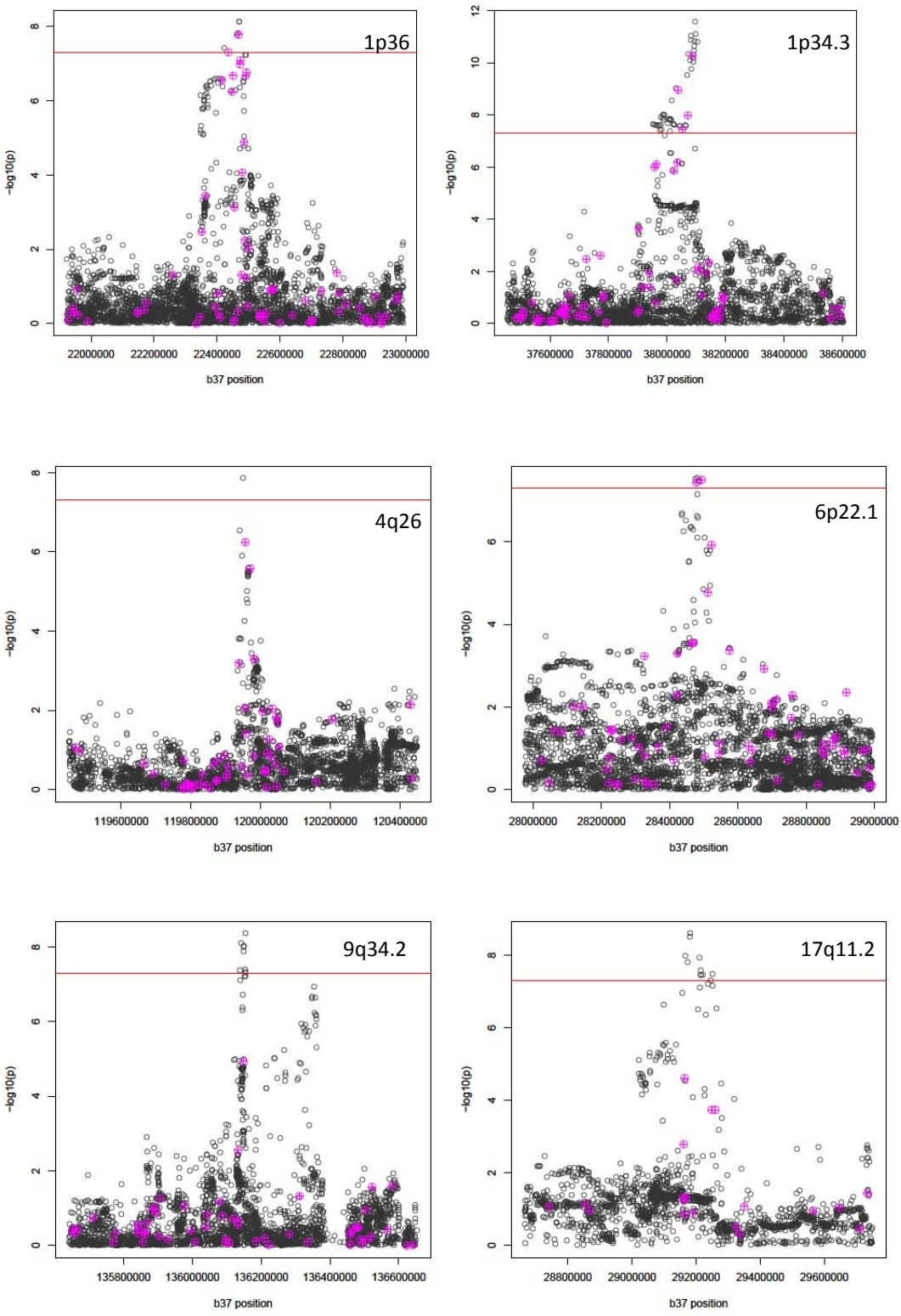
The left column on the left shows all variants and the right column shows variants not located in regions previously known to be associated with invasive ovarian cancer.



Supplementary Figure 4

Meta-analysis risk associations.

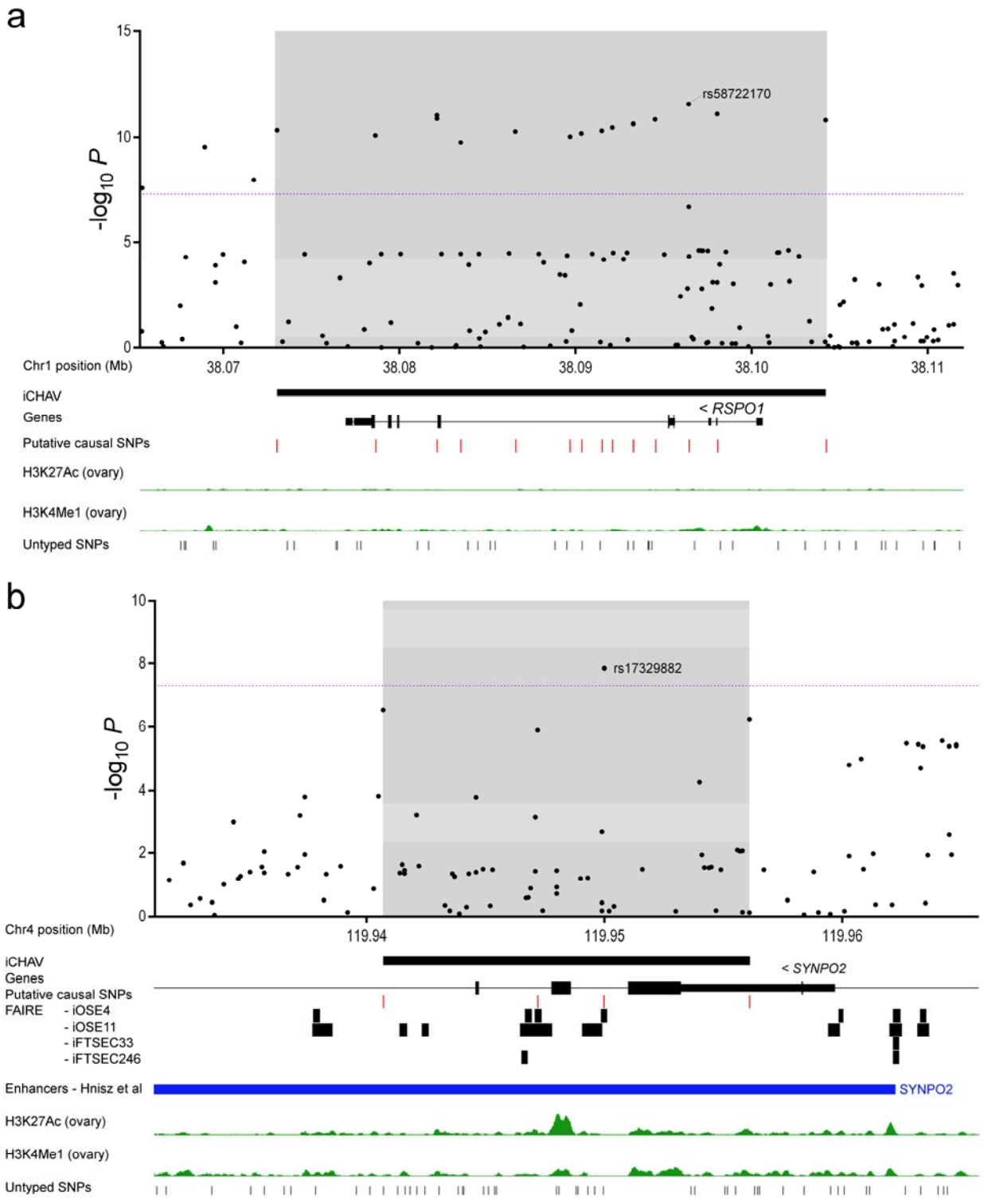
Manhattan plots showing the meta-analysis associations of genetic variants with risk of all subtypes of ovarian cancer (a, b) and serous subtype ovarian cancer (c, d) for all genetic variants available after the first imputation (a,c) and after excluding SNPs located within known ovarian cancer susceptibility loci (b,d).



Supplementary Figure 5.

Regional association plots for each novel locus based on the meta-analysis.

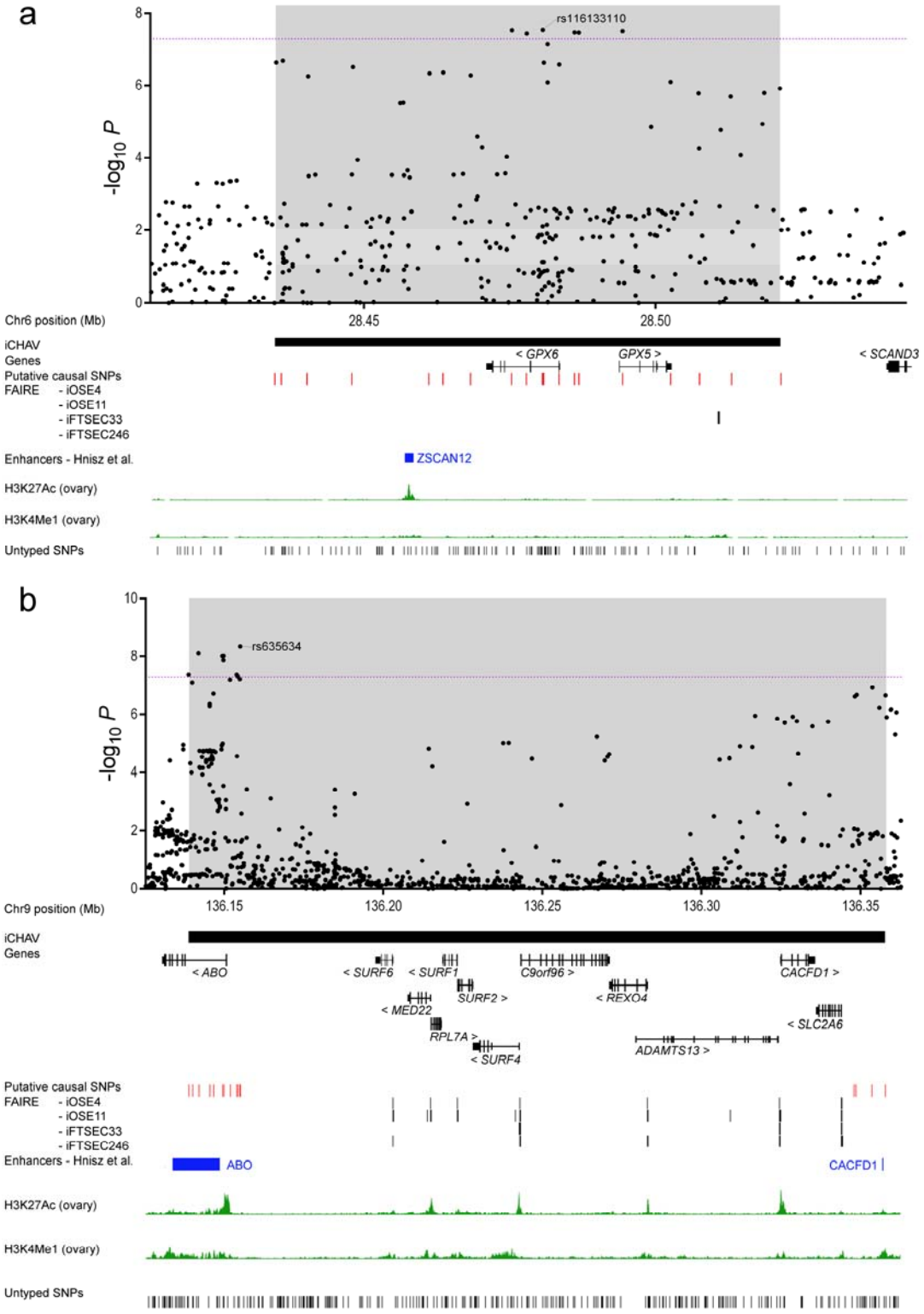
For 17q11.2 the meta-analysis was based on OCAC and BRCA2 mutation carriers only. For 1p34.3 and 6p22.1, the OCAC analysis was based on serous ovarian cancer. SNPs genotyped by the iCOGS array are shown in magenta and imputed SNPs in black.



Supplementary Figure 6

Ovarian cancer susceptibility loci at chromosome 1 and chromosome 4.

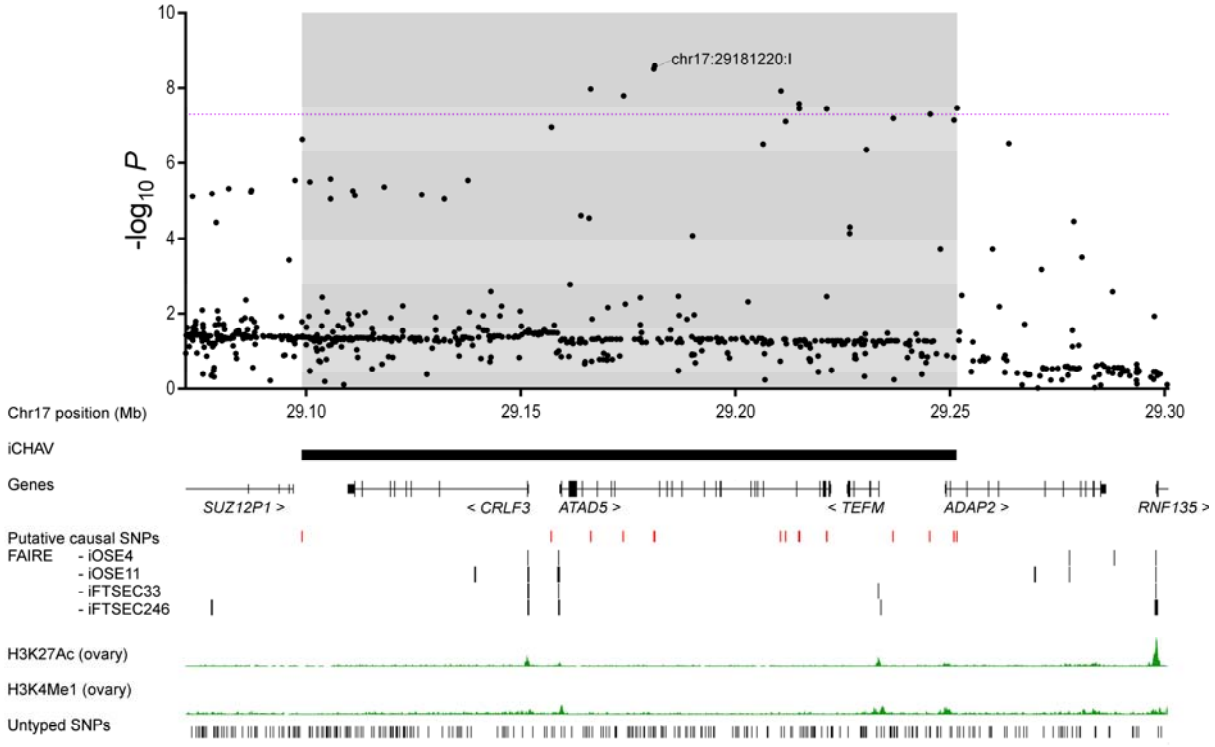
The Manhattan plot depicts the strength of association between all imputed and genotyped SNPs across the regions at chromosome 1 (a) and chromosome 4 (b). The dotted line represents the genome-wide significance level 5x10-8. FAIRE-seq data revealing potential regulatory regions in ovarian and fallopian tubes cells are depicted as black bars Additional tracks show genes and enhancers in ovary as described in Hnisz et al38. Positions of SNPs for which imputation r2<0.3 and/or minor allele frequency <0.005 are shown in the bottom track as 'untyped' SNPs.



Supplementary Figure 7

Ovarian cancer susceptibility loci at chromosome 6 and chromosome 9.

The Manhattan plot depicts the strength of association between all imputed and genotyped SNPs across the regions at chromosome 6 (a) and chromosome 9 (b). The dotted line represents the genome-wide significance level 5x10-8. FAIRE-seq data revealing potential regulatory regions in ovarian and fallopian tubes cells are depicted as black bars Additional tracks show genes and enhancers in ovary as described in Hnisz et al38. Positions of SNPs for which imputation r2<0.3 and/or minor allele frequency <0.005 are shown in the bottom track as 'untyped' SNPs.



Supplementary Figure 8

Ovarian cancer susceptibility locus at chromosome 17.

The Manhattan plot depicts the strength of association between all imputed and genotyped SNPs across the regions at chromosome 17. The dotted line represents the genome-wide significance level 5x10-8. FAIRE-seq data revealing potential regulatory regions in ovarian and fallopian tubes cells are depicted as black bars Additional tracks show genes and enhancers in ovary as described in Hnisz et al38. Positions of SNPs for which imputation r2<0.3 and/or minor allele frequency <0.005 are shown in the bottom track as 'untyped' SNPs.

Supplementary Table 1. Genotyping and imputation details for each study

Sample	N	Genotyping array	Genotyping centre	Imputation reference panel	Imputation software	Imputation QC filters
BRCA1 carriers	15,252	iCOGS	Mayo Clinic Medical Genome Facility	1000G v3 April 2012 CEU	IMP2 v2, SHAPEIT	MAF>0.005, r^2>0.3
BRCA2 carriers	8,211	iCOGS	McGill University and Génome Québec Innovation Centre	1000G v3 April 2012 CEU	IMP2 v2, SHAPEIT	MAF>0.005, r^2>0.3
OCAC-iCOGS	11,069 cases, 21,722 controls	iCOGS	McGill University and Génome Québec Innovation Centre and Mayo Clinic Medical Genome Facility	1000G v3 April 2012 CEU	IMP2 v2, SHAPEIT	r^2>0.25
UK GWAS	1,762 cases, 6,118 controls	Illumina 550K	Illumina	1000G v3 April 2012 CEU	IMP2 v2, SHAPEIT	r^2>0.25
Mayo GWAS	441 cases, 441 controls	HumanOmni2.5-8 BeadChip	Mayo Clinic Medical Genome Facility	1000G v3 April 2012 CEU	IMP2 v2, SHAPEIT	r^2>0.25
US GWAS	2,165 cases, 2,564 controls	Illumina 610-quad, 317K and 370K	POC and BWH at NCI and US at Mayo Clinic Medical Genome Facility	1000G v3 April 2012 CEU	minimac version 2012.8.15, mach version 1.0.18	r^2>0.25

Supplementary Table 2. Number of genetic variants that were genotyped and imputed on the 1000 Genomes Project data

	***BRCA1* carriers**	***BRCA2* carriers**	**OCAC-iCOGS**	**UK GWAS**	**US GWAS**	**U19**
Genotyped SNPs after QC	200,720	200,908	199,526	492,956	543,529*	1,587,051
Imputed, not monomorphic	16,436,671	16,254,607	15,533,199‡	15,521,891‡	15,524,649‡	15,134,200‡
Imputed, MAF[?]>0.05	6,717,256	6,747,730	6,947,385	6,928,746	6,936,998	6,954,339
Imputed, MAF[?]>0.005 & $r^{2¥}$>0.3	10,969,794	10,880,932	10,913,327	10,910,639	10,926,729	10,962,898

* With genotype data in any of the included studies

‡ In OCAC imputation was based on the 1000 Genomes Project data with singleton sites removed

[?] minor allele frequency

[¥] imputation accuracy r^2

Supplementary Table 3. ORs/HRs and tests of association for previously reported ovarian cancer susceptibility loci for ovarian cancer in *BRCA1* and *BRCA2* mutation carriers and for serous ovarian cancer in OCAC. Also shown are the tests of association from a meta-analysis between *BRCA1* and *BRCA2* mutation carriers and the general population samples

					OCAC serous					*BRCA1* carriers				*BRCA2* carriers				MA
Location	**Nearest gene**	**rs#**	**Ref[6]**	**Eff[6]**	**N ctrl[1] (EAF)**	**N case[2] (EAF)**	**EAF[7]**	**OR (95%CI)**	**P**	**N unaff.[1] (MAF)**	**N aff.[2] (MAF)**	**HR (95%CI)**	**P**	**N unaff.[1] (MAF)**	**N aff.[2] (MAF)**	**HR (95%CI)**	**P**	**p[3]**
9p22.2	*BNC2*	rs3814113	A	G	30845 (0.32)	9627 (0.28)	0.32	0.79 (0.76-0.82)	$2.7x10^{-34}$	12788 (0.34)	2461 (0.29)	0.78 (0.73-0.83)	$5.9x10^{-13}$	7579 (0.33)	631 (0.27)	0.74 (0.65-0.84)	$6.5x10^{-6}$	$5.6x10^{-50}$
8q24.21	*CMYC*	rs10088218	G	A	30845 (0.13)	9627 (0.11)	0.13	0.77 (0.73-0.82)	$1.6 x10^{-20}$	12790 (0.13)	2462 (0.13)	0.89 (0.81-0.97)	0.013	7580 (0.13)	631 (0.12)	0.87 (0.72-1.04)	0.13	$1.1 x10^{-20}$
2q31.1	*HOXD1*	rs2072590	C	A	30845 (0.68)	9627 (0.65)	0.68	1.14 (1.10-1.19)	$3.7 x10^{-13}$	12788 (0.32)	2461 (0.32)	1.03 (0.96-1.10)	0.36	7577 (0.31)	631 (0.35)	1.25 (1.11-1.42)	$6.6 x10^{-4}$	$9.4 x10^{-14}$
3q25.31	*TIPARP*	rs7651446	C	A	30845 (0.05)	9627 (0.08)	0.05	1.59 (1.48-1.70)	$1.5 x10^{-38}$	12789 (0.04)	2462 (0.06)	1.50 (1.31-1.72)	$4.1 x10^{-8}$	7579 (0.05)	631 (0.08)	1.94 (1.53-2.47)	$7.9 x10^{-9}$	$6.0 x10^{-51}$
19p13.11	*BABAM1*	rs8170	G	A	30845 (0.19)	9627 (0.21)	0.19	1.18 (1.13-1.23)	$2.9 x10^{-14}$	12781 (0.19)	2461 (0.18)	1.04*[4] (0.94-1.15)	0.47	7573 (0.18)	630 (0.21)	1.22*[4] (1.01-1.47)	0.041	$4.6 x10^{-14}$*[4]
17q21.32	*SKAP1*	rs9303542	A	G	30845 (0.27)	9627 (0.30)	0.27	1.14 (1.10-1.19)	$4.0 x10^{-12}$	12778 (0.27)	2460 (0.28)	1.13 (1.05-1.22)	$9.4 x10^{-4}$	7579 (0.27)	631 (0.30)	1.11 (0.97-1.26)	0.11	$4.9 x10^{-15}$
8q21.13	*CHMP4C*	rs11782652	A	G	30845 (0.07)	9627 (0.08)	0.07	1.24 (1.16-1.32)	$5.6 x10^{-11}$	12790 (0.07)	2462 (0.07)	1.08 (0.96-1.22)	0.17	7578 (0.07)	631 (0.08)	1.05 (0.84-1.30)	0.75	$2.5 x10^{-10}$
10p12.31	*MLLT10*	rs1243180	T	A	30845 (0.31)	9627 (0.33)	0.3	1.10 (1.06-1.14)	$3.3 x10^{-7}$	12770 (0.33)	2459 (0.34)	1.08 (1.01-1.16)	0.024	7576 (0.32)	631 (0.35)	1.19 (1.05-1.36)	$4.6 x10^{-3}$	$1.2 x10^{-9}$
17q12	*HNF1B*	rs757210	G	A	30845 (0.63)	9627 (0.61)	0.63	1.11 (1.07-1.15)	$8.2 x10^{-9}$	12781 (0.37)	2459 (0.37)	1.02 (0.96-1.09)	0.48	7574 (0.38)	631 (0.40)	1.12 (1.00-1.26)	0.10	$1.8 x10^{-8}$
5p15.33	*TERT*	rs10069690	G	A	30845 (0.26)	9627 (0.28)	0.27	1.14 (1.10-1.19)	$7.6 x10^{-11}$	12778 (0.28)	2456 (0.26)	0.97*[4] (0.89-1.06)	0.47	7568 (0.27)	630 (0.29)	1.11*[4] (0.95-1.29)	0.21	$8.5 x10^{-9}$*[4]
17q21.31	*PLEKHM1*	rs183211	G	A	30845 (0.24)	9627 (0.26)	0.23	1.11 (1.07-1.16)	$1.6 x10^{-7}$	12789 (0.23)	2462 (0.26)	1.19 (1.10-1.29)	$7.5 x10^{-6}$	7580 (0.25)	631 (0.30)	1.26 (1.10-1.43)	$9.5 x10^{-4}$	$1.9 x10^{-13}$
4q32.3*[5]	*TRIM61*	rs4691139	A	G	30845 (0.47)	9627 (0.48)	0.46	1.00 (0.97-1.03)	0.99	12790 (0.48)	2462 (0.52)	1.19 (1.12-1.26)	$7.2 x10^{-8}$	7577 (0.51)	630 (0.52)	1.08 (0.96-1.22)	0.22	0.028

[1] Number of women considered unaffected in the analysis of ovarian cancer associations

[2] Number of women considered affected in the analysis of ovarian cancer associations

[3] P-value from the meta-analysis of the association between the SNP and ovarian cancer in *BRCA1* and *BRCA2* carriers and serous ovarian cancer in OCAC

*[4] Ovarian cancer association in CIMBA estimated using a competing risks analysis which simultaneously models the association between ovarian and breast cancer.

*[5] Previous reports found no evidence of association in OCAC or *BRCA2* mutation carriers
[6] Reference and effect allele
[7] Effect allele frequency

Supplementary Table 4. Number of variants associated with ovarian cancer at different levels of p-values (proportion) after quality control

Sample	P<0.5	P<0.05	P<0.001	$P<10^{-5}$	$P<10^{-6}$	$P<10^{-7}$	$P<5x10^{-8}$
***BRCA1* carriers**							
Genotyped	102882 (0.513)	11792 (0.059)	667 (0.003)	202 (0.001)	116 ($6x10^{-4}$)	66 ($3x10^{-4}$)	50 ($3x10^{-4}$)
Imputed	5526028 (0.504)	568732 (0.052)	118984 (0.001)	848 ($7x10^{-5}$)	304 ($3x10^{-5}$)	172 ($2x10^{-5}$)	136 ($1x10^{-5}$)
Novel*	5483584 (0.503)	558979 (0.051)	11702 (0.001)	153 ($2x10^{-5}$)	26 ($3x10^{-6}$)	0	0
Novel*, R2>.7	2972747 (0.506)	307166 (0.052)	7005 (0.001)	90 ($2x10^{-5}$)	17 ($3x10^{-6}$)	0	0
Novel* regions	-	-	-	-	7	0	0
***BRCA2* carriers**							
Genotyped	101647 (0.506)	10668 (0.053)	520 (0.003)	161 ($8x10^{-4}$)	122 ($7x10^{-4}$)	118 ($6x10^{-4}$)	115 ($6x10^{-4}$)
Imputed	5501184 (0.504)	555821 (0.051)	17081 (0.002)	588 ($5x10^{-5}$)	304 ($3x10^{-5}$)	292 ($3x10^{-5}$)	283 ($3x10^{-5}$)
Novel*	5439848 (0.503)	545393 (0.051)	12945 (0.001)	192 ($2x10^{-5}$)	2 ($2x10^{-6}$)	0	0
Novel*, R2>.7	2964514 (0.504)	300836 (0.051)	7093 (0.001)	64 ($1x10^{-5}$)	2 ($7x10^{-7}$)	0	0
Novel* regions	-	-	-	-	2	0	0
OCAC COGS							
Genotyped	102523 (0.515)	12576 (0.063)	1164 (0.006)	484 (0.002)	376 (0.002)	244 (0.001)	215 (0.001)
Imputed	5528914 (0.507)	596736 (0.055)	20842 (0.002)	4302 ($4x10^{-4)}$)	3528 ($3x10^{-4}$)	730 ($7x10^{-5}$)	651 ($6x10^{-5}$)
Novel*	5485438 (0.506)	584249 (0.054)	15373 (0.001)	240 ($1x10^{-5}$)	16 ($2x10^{-6}$)	0	0
Novel*, R2>.7	3036532 (0.508)	332686 (0.056)	10352 (0.002)	196 ($3x10^{-5}$)	13 ($2x10^{-6}$)	0	0
Novel* regions	-	-	-	-	6	0	0
UKGWAS							
Genotyped	249051 (0.505)	26608 (0.054)	633 (0.001)	14 ($4x10^{-5}$)	6 ($1x10^{-5}$)	2 ($4x10^{-6}$)	0
Imputed	5503536 (0.504)	565227 (0.052)	12713 (0.001)	325 ($3x10^{-5}$)	194 ($2x10^{-5}$)	100 ($1x10^{-5}$)	30 ($3x10^{-6}$)
Novel*	5464447 (0.504)	559827 (0.052)	12079 (0.001)	92($9x10^{-6}$)	16 ($2x10^{-6}$)	4 ($4x10^{-7}$)	4 ($4x10^{-7}$)
Novel*, R2>.7	4696553 (0.505)	486266 (0.052)	10738 (0.001)	83 ($9x10^{-6}$)	16 ($2x10^{-6}$)	4 ($4x10^{-7}$)	4 ($4x10^{-7}$)
Novel* regions	-	-	-	-	4	1	1

U19							
Genotyped	803446 (0.505)	78352 (0.049)	1475 (0.001)	1 ($6x10^{-7}$)	0	0	0
Imputed	5514468 (0.503)	504874 (0.046)	9755 (0.001)	13 ($1x10^{-6}$)	1 ($9x10^{-8}$)	0	0
Novel*	5473821 (0.503)	496847 (0.046)	8542 (0.001)	13 ($1x10^{-6}$)	1 ($9x10^{-8}$)	0	0
Novel*, R2>.7	5005215 (0.502)	464721 (0.047)	8335 (0.001)	12 ($1x10^{-6}$)	0	0	0
Novel* regions	-	-	-	-	1	0	0
USGWAS							
Genotyped	273122 (0.502)	27486 (0.051)	544 (0.001)	7 ($1x10^{-5}$)	1 ($2x10^{-6}$)	0	0
Imputed	5495458 (0.503)	553573 (0.051)	9902 (0.001)	409 ($4x10^{-5}$)	132 ($1x10^{-5}$)	0	0
Novel*	5454727 (0.503)	545502 (0.050)	9246 (0.001)	56 ($5x10^{-6}$)	1 ($9x10^{-8}$)	0	0
Novel*, R2>.7	4557208 (0.503)	458029 (0.051)	7832 (0.001)	47 ($7x10^{-6}$)	0	0	0
Novel* regions	-	-	-	-	1	0	0
Meta-analysis OCAC, *BRCA1* and *BRCA2* carriers							
Imputed	5824308 (0.511)	650171 (0.057)	26121 (0.002)	6228 ($6x10^{-4}$)	5478 ($5x10^{-4}$)	5054 ($4x10^{-4}$)	4959 ($4x10^{-4}$)
Novel*	5752382 (0.510)	632753 (0.056)	18831 (0.002)	550 ($5x10^{-5}$)	176 ($2x10^{-5}$)	35 ($3x10^{-6}$)	24 ($2x10^{-6}$)
Novel* regions	-	-	-	-	12	5	4

* After removing SNPs located within 1 Mb of previously reported ovarian cancer susceptibility variants. For the locus at 17q21.31 we extended the region to about 1.8 Mb because of the strong LD structure in that region.

Supplementary Table 5. Association test results, HR/OR estimates and meta- analysis results for novel loci. Results reported for invasive ovarian cancer in *BRCA1* and *BRCA2* mutation carriers and ovarian cancer as well as serous subtype in OCAC. Results based on first imputation. SNP with smallest p-value reported for each locus

			OCAC all histologies			**OCAC serous**		***BRCA1* carriers**			***BRCA2* carriers**			**MA invasive[1]**	**MA serous[2]**
Location	**Nearest gene**	**rs#**	**r^2***	**OR (95%CI)**	**P**	**OR (95%CI)**	**P**	**r^2***	**HR (95%CI)**	**P**	**r^2***	**HR (95%CI)**	**P**	**P**	**P**
1p36	*WNT4*	rs3820282	1	1.11 (1.06-1.15)	$8.5x10^{-7}$	1.12 (1.07-1.17)	$3.3x10^{-6}$	1	1.14 (1.04-1.25)	$4.4x10^{-3}$	1	1.03 (0.87-1.23)	0.70	$2.0x10^{-8}$	$7.7x10^{-8}$
1p34.3	*RSPO1*	rs12039431	0.92	1.07 (1.03-1.11)	$4.4x10^{-4}$	1.11 (1.07-1.16)	$5.1x10^{-7}$	0.92	1.14 (1.06-1.23)	$6.1x10^{-4}$	0.92	1.29 (1.12-1.49)	$3.8x10^{-4}$	$1.1x10^{-8}$	$1.4x10^{-11}$
4q26	*SYNPO2*	rs17329882	0.95	1.09 (1.06-1.13)	$3.9x10^{-7}$	1.11 (1.07-1.16)	$2.7x10^{-7}$	0.95	1.07 (0.99-1.15)	0.08	0.95	1.14 (0.99-1.31)	0.08	$2.2 x10^{-8}$	$2.0x10^{-8}$
6p22.1	*GPX6*	rs115344852	1	0.94 (0.91-0.97)	$7.5x10^{-5}$	0.91 (0.87-0.94)	$2.7x10^{-7}$	1	0.92 (0.86-0.99)	0.024	1	0.97 (0.86-1.10)	0.65	$5.8x10^{-6}$	$3.2x10^{-8}$
9q34.2	*ABO*	chr9:136138765:D	0.74	1.15 (1.10-1.21)	$6.0x10^{-9}$	1.17 (1.11-1.24)	$2.4x10^{-8}$	0.75	1.12 (1.01-1.24)	0.032	0.75	0.94 (0.78-1.15)	0.56	$3.3x10^{-9}$	$2.0x10^{-8}$
16q21		rs8044477	0.73	1.10 (1.06-1.13)	$1.3x10^{-7}$	1.10 (1.06-1.15)	$2.2x10^{-6}$	0.75	1.08 (1.00-1.16)	0.047	0.75	1.08 (0.94-1.24)	0.27	$1.0x10^{-8}$	$1.7x10^{-7}$
17q11.2	*ATAD5*	chr17:29181220:I	0.97	0.90 (0.87-0.93)	$1.2x10^{-9}$	0.90 (0.86-0.94)	$1.3x10^{-7}$	0.97	1.02 (0.95-1.09)	0.62	0.97	0.92 (0.81-1.06)	0.24	$6.4x10^{-10}$*[3]	$6.8x10^{-8}$*[3]

* Imputation accuracy r^2 estimate

[1] P-value from the meta-analysis association test for ovarian cancer in OCAC and *BRCA1* and *BRCA2* carriers

[2] P-value from the meta-analysis association test for ovarian cancer in *BRCA1* and *BRCA2* carriers and serous ovarian cancer in OCAC

*[3] meta-analysis of ovarian cancer associations in *BRCA2* carriers and OCAC only

Supplementary Table 6. Ovarian cancer association tests in OCAC, *BRCA1* and *BRCA2* carriers and combined analysis for the most strongly associated genotyped SNP within a 500Mb region around the lead SNP of each novel locus

							OCAC			*BRCA1* carriers			*BRCA2* carriers			Meta-analysis*[1]
Locus	**SNP**	**Position**	**Ref**[*5]	**Eff**[*5]	**R^2*[2]**	**Lead SNP**	**HR (95%CI)**	**EAF**	**P**	**HR (95%CI)**	**EAF**	**P**	**HR (95%CI)**	**EAF**	**P**	**P**
1p36	rs3820282	22468215	T	C	0.94	rs56318008	1.11 (1.06-1.15)	0.15	$6.8x10^{-7}$	1.14 (1.04-1.25)	0.14	$4.4 x10^{-3}$	1.03 (0.87-1.22)	0.14	0.70	$1.6 x10^{-8}$
1q34.3	rs12023270	38086578	T	C	0.73	rs58722170	1.10 (1.06-1.14)	0.26	$2.7 x10^{-6}$*[3]	1.13 (1.05-1.21)	0.27	$5.3 x10^{-4}$	1.27 (1.12-1.44)	0.28	$1.2 x10^{-4}$	$5.3 x10^{-11}$*[3]
4q26	rs752097	119956089	A	G	0.86	rs17329882	1.08 (1.04-1.12)	0.23	$1.6 x10^{-5}$	1.08 (1.00-1.16)	0.24	0.051	1.12 (0.98-1.28)	0.23	0.08	$5.7 x10^{-7}$
6p22.1	rs445870	28494327	A	G	0.97	rs116133110	0.91 (0.87-0.94)	0.30	$2.5 x10^{-7}$*[3]	0.93 (0.86-1.00)	0.29	0.040	0.96 (0.84-1.09)	0.30	0.44	$3.2 x10^{-8}$*[3]
9q34.2	rs505922	136149229	T	C	0.39	rs635634	1.05 (1.02-1.09)	0.34	$6.5 x10^{-4}$	1.08 (1.02-1.16)	0.36	0.011	1.09 (0.97-1.23)	0.35	0.16	$1.2 x10^{-5}$
17q11.2	rs3764419	29164023	A	C	0.57	chr17:29181220:I	0.94 (0.91-0.97)	0.39	$3.6 x10^{-5}$	1.02 (0.95-1.08)	0.39	0.68	0.94 (0.83-1.07)	0.38	0.39	$2.5 x10^{-5}$*[4]

*[1] p-value for the meta-analysis of invasive ovarian cancer for OCAC, BRCA1 and BRCA2 carriers unless stated otherwise

*[2] R^2 for the correlation with the most strongly associated SNP for each region (SNPs shown adjacent column) based on data from the 1000 Genomes Project v3

*[3] results for association with serous ovarian cancer in OCAC

*[4] meta-analysis for results from OCAC and from BRCA2 mutation carriers

[*5] Reference and effect allele

Supplementary Table 7. Ovarian cancer association of the imputed lead SNP at the 17q11.2 locus and of a correlated (r^2=0.95) haplotype based on two genotyped SNPs using data from the samples genotyped on the iCOGS array (14,733 ovarian cancer cases and 23,480 controls from OCAC-COGS and from 7,562 unaffected and 623 affected *BRCA2* mutation carriers).

Variant	**OCAC-COGS**		***BRCA2* carriers**		**Meta-analysis**
	OR (95%CI)	**p**	**HR (95%CI)**	**p**	**p**
chr17:29181220:I	0.91 (0.88-0.94)	$1.9x10^{-8}$	0.92 (0.80-1.05)	0.23	$1.8x10^{-8}$
AA haplotype*	0.91 (0.88-0.95)	$1.1x10^{-7}$	0.92 (0.81-1.04)	0.19	$8.6x10^{-8}$

* AA haplotype based on genotyped SNPs rs9910051 (AT) and rs3764419 (CA)

Supplementary Table 8. CIMBA competing risks association test results and HR estimates for ovarian and breast cancer for the most significantly associated genotyped SNP from each novel locus. Genotyped SNP with smallest p-value reported for each locus

			BRCA1* carriers OC		***BRCA1* carriers BC***		***BRCA2* carriers OC***		***BRCA2* carriers BC***	
Location	**rs#**	**r^2***	**HR (95%CI)**	**P**	**HR (95%)**	**P**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**
1p36	rs3820282	0.94	1.12 (1.00-1.25)	0.052	1.01 (0.94-1.07)	0.87	1.03 (0.83-1.28)	0.77	1.02 (0.93-1.12)	0.66
1p34.3	rs12023270	0.73	1.10 (1.01-1.20)	0.037	0.98 (0.94-1.03)	0.49	1.29 (1.11-1.51)	$1.1x10^{-3}$	0.98 (0.92-1.05)	0.59
4q26	rs752097	0.86	1.07 (0.98-1.17)	0.15	0.98 (0.94-1.04)	0.54	1.17 (0.99-1.38)	0.054	0.99 (0.93-1.07)	0.87
6p22.1	rs445870	0.97	0.88 (0.81-0.97)	$6.6x10^{-3}$	0.99 (0.95-1.05)	0.82	0.99 (0.85-1.17)	0.98	0.99 (0.93-1.06)	0.75
9q34.2	rs505922	0.39	1.10 (1.01-1.19)	0.027	1.02 (0.97-1.06)	0.53	1.10 (0.95-1.27)	0.20	0.98 (0.92-1.04)	0.45
17q11.2	rs3764419	0.57	1.04 (0.96-1.12)	0.36	1.00 (0.96-1.05)	0.99	0.93 (0.81-1.08)	0.36	0.95 (0.89-1.01)	0.09

* BC = breast cancer, OC = ovarian cancer

Supplementary Table 9. Pupasuite data for all putative causal SNPs

loci	SNP	chromosome	position	MinFreq	MaxFreq	pupasuite position *	pupasuite results	pupasuite results
1p36	rs12407439	1	22347396	0.84	0.86	UPSTREAM		
1p36	rs111992780	1	22361229	0.15	0.17			
1p36	rs12405695	1	22365689	0.15	0.16	INTERGENIC		
1p36	rs10799731	1	22365829	0.84	0.85	INTERGENIC		
1p36	rs10917128	1	22366102	0.84	0.85	INTERGENIC		
1p36	rs72665317	1	22367073	0.83	0.85	INTERGENIC		
1p36	rs10917130	1	22371065	0.84	0.85	INTERGENIC		
1p36	rs725158	1	22378280	0.15	0.17	UPSTREAM		
1p36	rs3754496	1	22378880	0.16	0.17	UPSTREAM		
1p36	chr1:22381399:D	1	22381399	0.20	0.21			
1p36	rs17837951	1	22388872	0.15	0.17	INTRONIC		
1p36	chr1:22396288:D	1	22396288	0.16	0.17			
1p36	rs12038474	1	22403357	0.16	0.17	INTRONIC		
1p36	chr1:22407102:D	1	22407102	0.83	0.85			
1p36	rs2268179	1	22414785	0.16	0.17	INTRONIC	conserved region	
1p36	rs2268177	1	22415410	0.83	0.85	INTRONIC	conserved region	
1p36	chr1:22418260:I	1	22418260	0.15	0.17			
1p36	rs10917151	1	22422721	0.14	0.16	DOWNSTREAM		
1p36	rs7412010	1	22436446	0.14	0.16	INTERGENIC		
1p36	rs10737462	1	22444975	0.20	0.22	DOWNSTREAM	conserved region	
1p36	rs3765350	1	22447316	0.78	0.80	INTRONIC	conserved region	
1p36	rs2235529	1	22450487	0.14	0.15	INTRONIC	conserved region	
1p36	rs12404660	1	22458794	0.81	0.83	INTRONIC	conserved region	
1p36	rs12037376	1	22462111	0.14	0.15	INTRONIC	conserved region	
1p36	rs61768001	1	22465820	0.85	0.86	INTRONIC	conserved region	triplex
1p36	rs3820282	1	22468215	0.14	0.15	INTRONIC	conserved region	

1p36	rs56318008	1	22470407	0.13	0.15	5PRIME_UTR	conserved region
1p36	rs55938609	1	22470451	0.13	0.15	5PRIME_UTR	conserved region
1p36	rs7519889	1	22472506	0.20	0.20	UPSTREAM	
1p36	rs12042083	1	22472732	0.20	0.20	UPSTREAM	conserved region
1p36	rs7515106	1	22473410	0.79	0.80	UPSTREAM	
1p36	rs12410251	1	22482629	0.19	0.20	INTERGENIC	
1p36	chr1:22483649:I	1	22483649	0.75	0.77		
1p36	rs3971300	1	22484575	0.73	0.74	INTERGENIC	
1p36	rs56104760	1	22486029	0.82	0.84	INTERGENIC	
1p36	rs72478520	1	22489567	0.16	0.18	INTERGENIC	
1p36	rs7521902	1	22490724	0.21	0.23	INTERGENIC	
1p36	rs4654785	1	22491843	0.76	0.78	INTERGENIC	
1p36	rs3920498	1	22492887	0.18	0.20	INTERGENIC	conserved region
1p34.3	rs61776206	1	38073048	0.24	0.26	DOWNSTREAM	conserved region
1p34.3	rs55852308	1	38078630	0.72	0.74	INTRONIC	conserved region
1p34.3	rs12039431	1	38082122	0.23	0.24	INTRONIC	conserved region
1p34.3	rs12046650	1	38082123	0.23	0.25	INTRONIC	conserved region
1p34.3	rs72659423	1	38083472	0.26	0.28	INTRONIC	
1p34.3	rs12023270	1	38086578	0.26	0.28	INTRONIC	
1p34.3	rs61776208	1	38089683	0.26	0.28	INTRONIC	
1p34.3	rs61776209	1	38090323	0.26	0.28	INTRONIC	
1p34.3	rs61776210	1	38091488	0.26	0.28	INTRONIC	
1p34.3	rs4073473	1	38092075	0.26	0.28	INTRONIC	
1p34.3	rs61776211	1	38093277	0.26	0.28	INTRONIC	
1p34.3	rs61776212	1	38094512	0.73	0.74	INTRONIC	
1p34.3	rs58722170	1	38096421	0.23	0.24	INTRONIC	conserved region
1p34.3	rs4335340	1	38098035	0.73	0.74	INTRONIC	conserved region
1p34.3	rs12120061	1	38104194	0.25	0.25	UPSTREAM	
4q26	chr4:119940713:D	4	119940713	0.74	0.75		
4q26	rs7671665	4	119947188	0.67	0.69	INTRONIC	conserved region
4q26	rs17329882	4	119949960	0.76	0.77	INTRONIC	conserved region
4q26	rs752097	4	119956089	0.23	0.24	3PRIME_UTR	conserved region

6p22.1	rs2191035	6	28434943	0.71	0.72	INTERGENIC	
6p22.1	rs2531815	6	28436060	0.28	0.29	INTERGENIC	
6p22.1	rs1016069	6	28440418	0.25	0.26	INTERGENIC	
6p22.1	rs1015811	6	28448086	0.75	0.75	UPSTREAM	
6p22.1	rs2859355	6	28461221	0.30	0.32	INTERGENIC	
6p22.1	rs2227228	6	28463576	0.68	0.70	INTERGENIC	conserved region
6p22.1	rs2531822	6	28468301	0.30	0.32	DOWNSTREAM	
6p22.1	rs7743046	6	28475368	0.29	0.31	INTRONIC	
6p22.1	rs4713167	6	28477895	0.69	0.71	INTRONIC	conserved region
6p22.1	rs116133110	6	28480635	0.69	0.71		
6p22.1	rs115095247	6	28480833	0.68	0.69		
6p22.1	chr6:28481485:D	6	28481485	0.27	0.29		
6p22.1	chr6:28481486:D	6	28481486	0.30	0.31		
6p22.1	rs116131800	6	28483482	0.68	0.69		
6p22.1	rs115344852	6	28486098	0.69	0.71		
6p22.1	rs115771114	6	28486822	0.69	0.71		
6p22.1	rs445870	6	28494327	0.70	0.71	INTRONIC	conserved region
6p22.1	rs115878751	6	28502550	0.71	0.72		
6p22.1	rs114159316	6	28507379	0.76	0.77		
6p22.1	rs115769866	6	28512882	0.22	0.23		
6p22.1	chr6:28518640:D	6	28518640	0.23	0.24		
6p22.1	rs393414	6	28521316	0.22	0.23	INTERGENIC	
9q34.2	chr9:136138765:D	9	136138765	0.14	0.14		
9q34.2	chr9:136139907:D	9	136139907	0.26	0.27		
9q34.2	rs2519093	9	136141870	0.19	0.20	INTRONIC	
9q34.2	rs9411378	9	136145425	0.23	0.23	INTRONIC	
9q34.2	rs550057	9	136146597	0.26	0.27	INTRONIC	
9q34.2	rs507666	9	136149399	0.19	0.20	INTRONIC	
9q34.2	chr9:136149709:D	9	136149709	0.18	0.19		
9q34.2	rs532436	9	136149830	0.19	0.20	INTRONIC	
9q34.2	rs600038	9	136151806	0.78	0.79	UPSTREAM	
9q34.2	rs651007	9	136153875	0.21	0.22	UPSTREAM	

9q34.2	rs579459	9	136154168	0.78	0.79	UPSTREAM	
9q34.2	rs649129	9	136154304	0.21	0.22	UPSTREAM	
9q34.2	rs495828	9	136154867	0.21	0.22	UPSTREAM	
9q34.2	rs635634	9	136155000	0.19	0.20	UPSTREAM	
9q34.2	rs56963659	9	136348194	0.10	0.12	UPSTREAM	
9q34.2	rs73550898	9	136348753	0.10	0.11	UPSTREAM	
9q34.2	rs7875786	9	136353663	0.10	0.11	INTERGENIC	
9q34.2	rs7864157	9	136357925	0.10	0.11	INTERGENIC	
17q11.2	rs9900596	17	29099077	0.82	0.83	INTERGENIC	
17q11.2	rs74815160	17	29157158	0.80	0.82		
17q11.2	rs62070643	17	29166302	0.73	0.74	INTRONIC	
17q11.2	rs62070644	17	29173948	0.26	0.27	INTRONIC	
17q11.2	rs62070645	17	29180996	0.25	0.27	INTRONIC	
17q11.2	chr17:29181220:I	17	29181220	0.72	0.74		
17q11.2	rs62070648	17	29210595	0.26	0.27	INTRONIC	
17q11.2	rs7223535	17	29211667	0.26	0.27	INTRONIC	
17q11.2	rs111305917	17	29214795	0.73	0.74		
17q11.2	rs113934718	17	29214880	0.26	0.27		
17q11.2	rs62070651	17	29214896	0.73	0.74	INTRONIC	
17q11.2	rs62070652	17	29221277	0.26	0.27	INTRONIC	conserved region
17q11.2	rs35958868	17	29236745	0.26	0.27	UPSTREAM	
17q11.2	rs62068770	17	29245375	0.73	0.74	UPSTREAM	
17q11.2	rs11867227	17	29250911	0.26	0.27	INTRONIC	
17q11.2	rs35840638	17	29251641	0.25	0.27	INTRONIC	conserved region

* Only SNPs with rs numbers could be analyzed but, even for those, position output was not available for all. http://pupasuite.bioinfo.cipf.es

Supplementary Table 10. Index SNPs at each of the novel loci, and biofeatures of putatively causal SNPs at each locus

Chr.	Closest Gene	Position of index SNPs	No. putatively causal SNPs	kb window	All genes in window	No. putatively causal SNPs aligned with biofeatures	putatively causal SNP with biofeatures	Location	Chromatin mark	Cell type
1p36	*WNT4*	promoter region of *WNT4*	39	145	*WNT4, CDC42, LINC00339*	11	rs72665317	Intergenic	H3K4me1	Mainly in OSECs/ FTSECs
							rs10917130	Intergenic *CDC42*	H3K4me1	Mainly OSECs/ FTSECs, some CaOV3
							rs725158	promoter *CDC42*	H3K4me1 FAIRE, H3K27ac,	Only in ENCODE FAIRE/H3K4me1 mainly in
							rs3754496	promoter *CDC42*	H3K4me1 H3K27ac,	OSECs/ FTSECs Only in OSECs/
							rs2268177	intron	H3K4me1 H3K27ac,	FTSECs
							rs10917151	Intergenic	H3K4me1	Only in OSECs
							rs2092322	Intergenic *WNT4*	H3K4me1	Only OSE11
							rs10737462	3'UTR *WNT4*	H3K4me1 H3K27ac,	Only in FTE33 Mainly in
							rs12404660	intron *WNT4*	H3K4me1 H3K27ac,	OSECs/ FTSECs Very strong in
							rs56318008	promoter	H3K4me1	CaOV3
							rs55938609	*WNT4*	H3K27ac,	Very strong in

								promoter	H3K4me1	CaOV3
1p34.3	*RSPO1*	intron 3 of *RSPO1*	15	31	*RSPO1*	0				
4q26	*SYNPO2*	intron 3 of *SYNPO2*	4	35	*SYNPO2*	2	rs7671665 rs17329882	*SYNPO2* intron *SYNPO2* intron	FAIRE, H3K27ac, H3K4me1 FAIRE, H3K27ac	H3K4me1 only in OSECs/ FTSECs Only in OSECs
6p22.1	*GPX6*	intron 1 of *GPX6*	22	130	*GPX6, GPX5*	1	rs115878751	*GPX5* 3'UTR	none	N/A
9q34.2	*ABO*	4.3kb upstream of *ABO* TSS	18	329*	***ABO**, SURF6, MED22, RPL7A, SNORD24, SNORD36B, SNORD36A, SNORD36C, SURF1, SURF2, SURF4, C9orf96, REXO4, ADAMTS13, CACFD1, **SLC2A6***	1	rs532436	*ABO* intron	H3H3K27 ac, H3K4me1	Only in CaOV3
17q11.2	*ATAD5*	intron 6 of *ATAD5*	16	229	*ATAD5, TEFM, ADAP2, CRLF3, SUZ12P1*	0				

* SNPs in this large window are either within or upstream of ABO or upstream of SLC2A6. Bold indicates these genes in gene list. None indicates no SNPs overlapped with biofeatures. N/A is not applicable. TSS = transcription start site

Supplementary Table 11. Summary of TCGA tumor data for all the genes in 1MB region around the top SNP at each locus

chr region	1p36	1p34.3	4q26	6p22.1	9q34.2	17q11.2
1MB region around top SNP	chr1:21970407-22970407	chr1:37596421-38596421	chr4:119449960-120449960	chr6:27980635-28980635	chr9:135655000-136655000	chr17:28681220-29681220
# genes in 1MB region	11	22	12	23	32	17
Closest gene	*WNT4*	*RSPO1*	*SYNPO2*	*GPX6*	*ABO*	*ATAD5*
Genes with potentially deleterious mutations in TCGA ovary tumors		*EPHA10*		*GPX6, TRIM27*	*TSC1, RALGDS, ABO, SURF1, C9orf96, ADAMTSL2*	*NF1*
Genes with only missense mutations in TCGA ovary tumors	*RAP1GAP, USP48, HSPG2, WNT4, ZBTB40*	*ZC3H12A, DNALI1, GNL2, MTF1, INPP5B*	*SYNPO2, USP53, FABP2*	*ZKSCAN4, NKAPL, ZSCAN26, PGBD1, ZSCAN31, SCAND3*	*MED22, REXO4, ADAMTS13, DBH, VAV2*	*GOSR1, ATAD5, TEFM, ADAP2, OMG, EVI2B, EVI2A*
Known genes catologued by Sanger Cancer Gene Census				*TRIM27*	*TSC1, RALGDS*	*NF1*
Cancer genes from literature	*WNT4, RAP1GAP, CDC42*	*RSPO1, C1orf109, FHL3*	*SYNPO2*	*ZKSCAN3, TRIM27*	*TSC1, ABO, RPL7A, VAV2*	*ATAD5, NF1*
Role/tissue type gene 1	*WNT4: inhibits cell growth in tumor cell lines*	*RSPO1*: essential malignancy + early ovary development	*SYNPO2*: TSG prostate, bladder + colon	*ZKSCAN3*: novel 'driver' colon, cell migration prostate	*ABO*: SNP association risk pancreas, ovary	*ATAD5*: predisposition, genetic and functional defects
Role/tissue type gene 2	*CDC42*: migration + signaling ovary, migration breast	*C1orf109*: cancer cell proliferation		*TRIM27*: cancer development, outcome endometrial	*TSC1*: SNP association breast	*NF1*: mutations neurofibromatosis type 1
Role/tissue type	*RAP1GAP*: TSG	*FHL3*:			*RALGDS*: Ras-	

gene 3	Thyroid + Pancreas	downregulation + antiproliferative breast			related GTPases, translocations lymphoma	
Role/tissue type gene 4					*RPL7A*: prostate + breast *VAV2*: Vav2-dependent activation RhoA GTPase breast	
Role/tissue type gene 5						
Potentially cancer related genes based on function	*WNT4, EPHA8*	*MEAF6, SNIP1, CDCA8, EPHA10*				
% GAIN DNA copy number	21	44	11.2	43	11.2	4.2
% LOSS DNA copy number	42	14	68	20	59.4	83.6
Genes with expression increased in tumors		*MEAF6, SNIP1, GNL2, C1orf109, CDCA8, YRDC, INPP5B, UTP11L, SF3A3*	*CEP170P1, SEC24D*	*ZNF165, ZSCAN16, ZKSCAN4, PGBD1, ZKSCAN3, ZSCAN9, ZSCAN31, ZSCAN12, ZNF311*	*SURF4, REXO4, VAV2*	*ATAD5*
Genes with expression decreased in tumors	*LDLRAD2, CELA3A, WNT4, EPHA8*	*DNALI1, RSPO1, EPHA10, POU3F1*	*SYNPO2, PDE5A, MYOZ2, USP53*	*NKAPL*	*C9orf9, RALGDS, GBGT1, ABO, RPL7A, TSC1, GFI1B, CEL, CELP, MED22, SURF1*	*CPD, NF1, GOSR1, RNF135*

Genes indicated in bold are the closest gene to the top risk SNP.
Genes underlined did not have consistent expression results on all platforms on which they were included.

Supplementary Table 12. TCGA tumor data and eQTL analysis in normal and tumor samples for the closest gene to each SNP

chr region	1p36	1p34.3	4q26	6p22.1	9q34.2	17q11.2
1MB region around top SNP	chr1:21970407-22970407	chr1:37596421-38596421	chr4:11944 9960-120449960	chr6:2798 0635-28980635	chr9:1356 55000-136655000	chr17:28681 220-29681220
# genes in 1MB region	11	22	12	23	32	17
closest gene	*WNT4*	*RSPO1*	*SYNPO2*	*GPX6*	*ABO*	*ATAD5*
# and type mutations	1 missense	0	1 missense	1 nonsense, 2 missense	1 splice	3 missense
% GAIN DNA copy number	21	44	11.2	43	11.2	4.2
% LOSS DNA copy number	42	14	68	20	59.4	83.6
% diploid DNA copy number	37.0	42.0	20.8	37.0	29.4	12.2
exp increase with copy #	NO	YES amp	NO	NO	NO	YES
TCGA_HT Expression tumor vs normal and p-value	down 0.032	ND	ND	ND	down 2E-05	up 3E-06
TCGA_agilent Expression tumor vs normal and p-value	down 0.193	down 0.341	ND	no difference 0.43	down 0.025	up 3E-06
TCGA_HuEx Expression tumor vs normal and p-value	down 6E-05	down 0.048	down 2E-06	no difference 0.13	down 2E-05	up 3E-06
summary expression result p-value	down in 2 of 3 platforms	down in 1 of 2 platforms	down 1 of 1 platforms	no difference 2 of 2 platforms	down 3 of 3 platforms	up 3 of 3 platforms
significance	average	low	high	no difference	high	high
Known role in cancer / tissue type	in WNT signaling pathway	RSPO1: essential malignancy + early ovary development	SYNPO2: TSG prostate, bladder + colon	none	ABO: SNP association risk pancreas, ovary	ATAD5: predisposition, genetic and functional defects

eQTL SNP TCGA tumors	rs2268177	N/A	N/A	N/A	rs651007	N/A
p-value TCGA 3 groups (n=339)	0.833	N/A	N/A	N/A	0.0653	N/A
eQTL SNP in OSECs and FTSECs	rs3820282	rs12023270	rs752097		rs505922	rs3764419
p-value OSECs 3 groups (n=54)	0.854	0.373	0.128	N/A	0.495	0.697
p-value OSECs 2 groups (n=54)	0.734	0.661	0.232	N/A	0.457	0.873
p-value All 3 groups (n=59)	0.568	N/A	0.0896*	N/A	N/A	N/A
p-value All 2 groups (n=59)	0.666	N/A	0.148	N/A	N/A	N/A

N/A indicates no expression of *GPX6* in OSECs and FTSECs or that there was a difference in expression between OSECs and FTSECs so the data was not combined.
ND indicates that there is no expression data because the gene failed quality control on that platform
* After exclusion of outliers, p-value was 0.067.

Supplementary Note

Imputation results

Imputation was carried out separately for *BRCA1* carriers, *BRCA2* carriers, OCAC-iCOGS samples and the three OCAC GWAS (**Supplementary Table 1**). For the studies using the iCOGS array, 99.1-99.5% of the 6.7M common variants (MAF>0.05) from the 1000 Genomes Project were imputed with imputation accuracy of >0.30 whereas 89.3-90.4% of rare SNPs (MAF ≤0.05) had imputation accuracy of >0.30 (**Supplementary Fig. 1, Supplementary Table 2**). 67.2-67.3% of the common variants were imputed with accuracy >0.7 for the samples genotyped on iCOGS but only 18.5-21.9% of the rare variants. The GWAS studies captured 99.7-99.9% of the common variants with imputation r2>0.3 and 84.2-90.8% of the rare variants while 94.8-97.8% of the common and 44.5-58.5% of the rare SNPs had imputation accuracy >0.7 (**Supplementary Fig. 2, Supplementary Table 2**).

The genomic inflation factor λ for the combined meta-analysis analysis was 1.18 (adjusted value to 1000 cases and controls λ_{1000}=1.01, **Supplementary Fig. 3G**). After excluding known susceptibility regions, there was little evidence of significant associations with ovarian cancer beyond that expected by chance in any of the individual studies (**Supplementary Fig. 3A-F**). However, in the CIMBA-OCAC meta-analysis we saw strong evidence of significant associations. After excluding known ovarian cancer susceptibility loci, 24 SNPs from four different regions were associated at genome-wide significance ($p<5x10^{-8}$) (**Supplementary Fig. 4, Supplementary Table 4**). Moreover, 176 SNPs from 12 different loci had p-values less than 10^{-6}.

Associations after excluding sample overlaps between OCAC and CIMBA

The primary analyses of the OCAC and CIMBA data were carried out independently. After completing the meta-analysis we identified 143 duplicates by comparing genotypes of *BRCA1* and *BRCA2* carriers with samples in OCAC. We then excluded these samples from OCAC and repeated the association analysis for the most strongly associated variant from each novel locus associated at genome-wide significance ($p<5x10^{-8}$). We then repeated the combined analysis of associations in OCAC, *BRCA1* and *BRCA2* mutation carriers as described above in order to assess whether sample overlap influenced the association results. The associations were consistent with the analysis before excluding overlaps. All SNPs remained associated with ovarian cancer risk in the combined analysis for OCAC, *BRCA1* and *BRCA2* carriers with $p<5x10^{-8}$.

Genotyping coverage

We also evaluated the level of coverage of common variation at each putative novel locus from our genotyping and imputation in relation to all the variants contained in the 1000 Genomes Project v3 data. Using the 1000 Genomes Project v3 we determined LD decay around the most strongly associated SNP (the lead SNP) in each region. For each region, the boundaries were set such that they contain all SNPs with $r^2 \geq 0.1$ with the lead SNP. Using pairwise tagging in Haploview [1] and data from the 1000 Genomes Project v3 we identified a set of LD blocks such that each SNP in the region was captured with $r^2 \geq 0.8$. For each LD block we evaluated whether any of the SNPs were genotyped

or imputed with moderate imputation accuracy (0.5< imputation r^2 ≤0.7) and high imputation accuracy (imputation r^2 >0.7) in the final meta-analysis results. Indels were not included.

We found that we had genotyped or imputed data covering 91% of the genetic variation in the region around the most strongly associated SNP at 1p36. For the locus at 1p34.3 the coverage was 84%, and for the locus at 4q26 the coverage was 83%. For each of these three signals we covered all common SNPs with MAF<5% based on the 1000 Genomes Project data. The other three novel loci had coverage of less than 80%. However, for each of the regions, all linkage disequilibrium blocks containing at least five SNPs were captured, apart from two exceptions.

Imputation accuracy of lead SNPs for novel loci

The most significantly associated SNP at each of the six novel loci had high imputation accuracy (r^2≥0.83). At the 1p34.3, 1p36, and 6p22.1 loci, there was at least one genotyped SNP, correlated with the lead SNP (pairwise r2≥0.73), which was also associated at genome-wide significance level in the meta-analysis (**Supplementary Table 6**). At the other loci the most strongly associated genotyped SNPs displayed p-values between $3x10^{-5}$ and $6x10^{-7}$, and their correlation to the respective lead SNP was between 0.39 and 0.86. To evaluate imputation accuracy for each of these three loci, we genotyped each lead SNP in a subset of samples using iPLEX and compared the imputed genotypes with the observed genotypes. Genotype data were available for 1,949 *BRCA1* and 1,350 *BRCA2* mutation carriers after quality control for the lead SNP, rs17329882, at 4q26. When we compared the genotypes with the dosages from the imputation, we found a coefficient of determination of r^2 =0.90. These values were consistent with the estimated imputation accuracy of r^2 =0.93 from the imputation. SNP rs635634 at 6p22.1 was genotyped in 1,420 *BRCA1* and 1,004 *BRCA2* carriers and the genotypes were compared with the dosages from the imputation. The coefficient of determination was r^2 =0.84 which is consistent with the estimated imputation accuracy of r^2 =0.83.The lead SNP at 17q11.2, chr17:29181220:I failed iPLEX design.

Competing risks analyses in *BRCA1* and *BRCA2* mutation carriers

We also assessed whether any of the novel ovarian cancer susceptibility loci were associated with breast cancer risk for *BRCA1* and *BRCA2* mutation carriers. The analysis was carried out within a competing risks framework by estimating the associations with breast and ovarian cancer risk simultaneously [2,3]. A different censoring process was used for this analysis. Individuals were followed up to the age of breast or ovarian cancer diagnosis, whichever occurred first, and were considered affected for the respective disease. Mutation carriers were censored at bilateral prophylactic mastectomy for breast and RRSO for ovarian cancer and were assumed to be unaffected for the corresponding disease. The most strongly associated genotyped SNPs at each locus were used for this purpose because the analysis software requires genotyped data.

The HR estimates for the association with ovarian cancer in the competing risks analysis were consistent with the estimates from the main analysis for all SNPs (**Supplementary Table 8**). None of the SNPs displayed associations with breast cancer risk at p<0.05.

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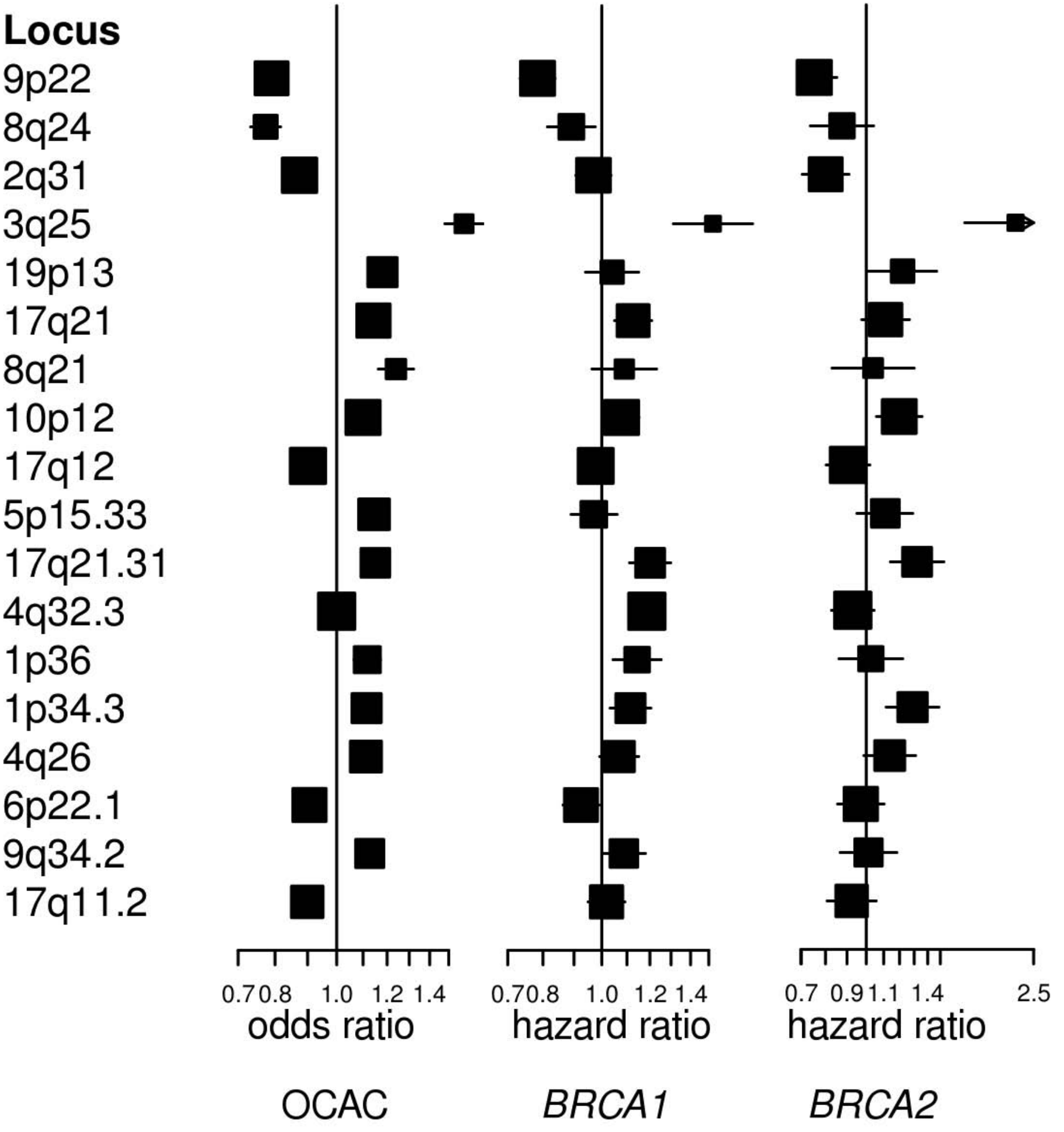
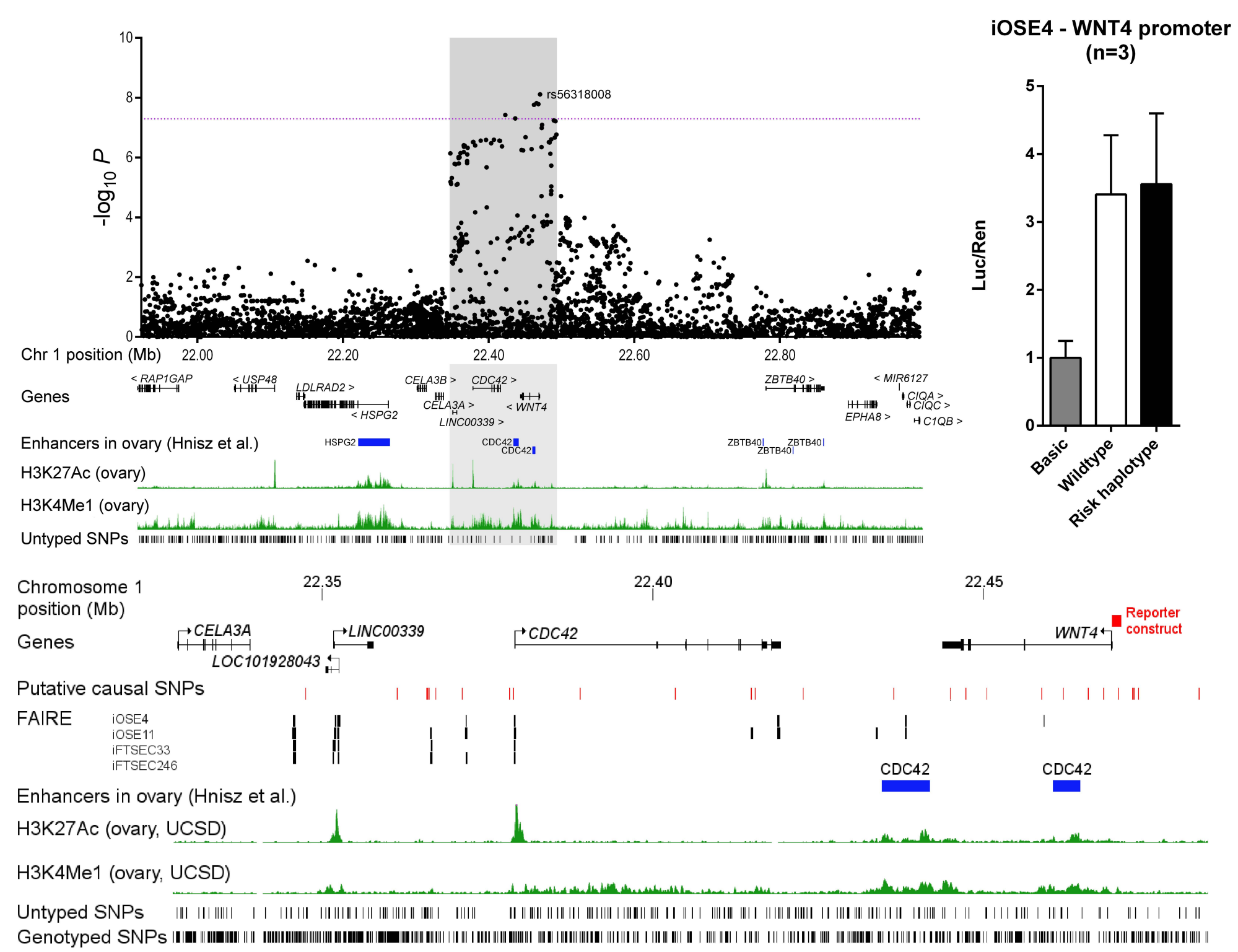

Locus
9p22
8q24
2q31
3q25
19p13
17q21
8q21
10p12
17q12
5p15.33
17q21.31
4q32.3
1p36
1p34.3
4q26
6p22.1
9q34.2
17q11.2
0.7 0.8 1.0 1.2 1.4
odds ratio
0.7 0.8 1.0 1.2 1.4
hazard ratio
0.7 0.9 1.1 1.4 2.5
hazard ratio
OCAC
BRCA1
BRCA2


iOSE4 - WNT4 promoter
(n=3)
Luc/Ren
Basic
Wildtype
Risk haplotype
rs56318008
-log10 P
Chr 1 position (Mb)
22.00
22.20
22.40
22.60
22.80
Genes
< RAP1GAP
< USP48
LDLRAD2 >
< HSPG2
CELA3B >
CDC42 >
CELA3A >
LINC00339 >
< WNT4
ZBTB40 >
< MIR6127
CIQA >
CIQC >
EPHA8 >
C1QB >
Enhancers in ovary (Hnisz et al.)
HSPG2
CDC42
ZBTB40
H3K27Ac (ovary)
H3K4Me1 (ovary)
Untyped SNPs
Chromosome 1
position (Mb)
22.35
22.40
22.45
Genes
CELA3A
LOC101928043
LINC00339
CDC42
WNT4
Reporter
construct
Putative causal SNPs
FAIRE
iOSE4
iOSE11
iFTSEC33
iFTSEC246
CDC42
CDC42
Enhancers in ovary (Hnisz et al.)
H3K27Ac (ovary, UCSD)
H3K4Me1 (ovary, UCSD)
Untyped SNPs
Genotyped SNPs