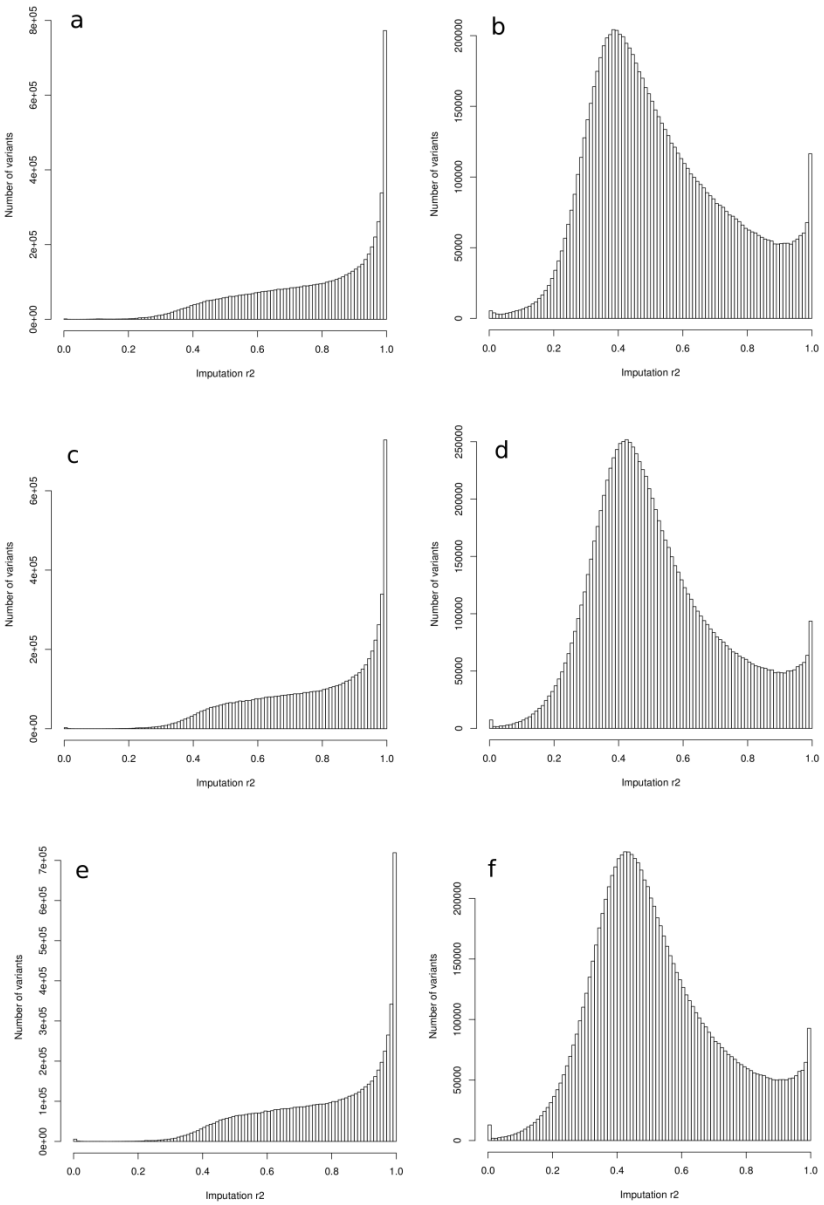
Identification of six new susceptibility loci for invasive epithelial ovarian cancer

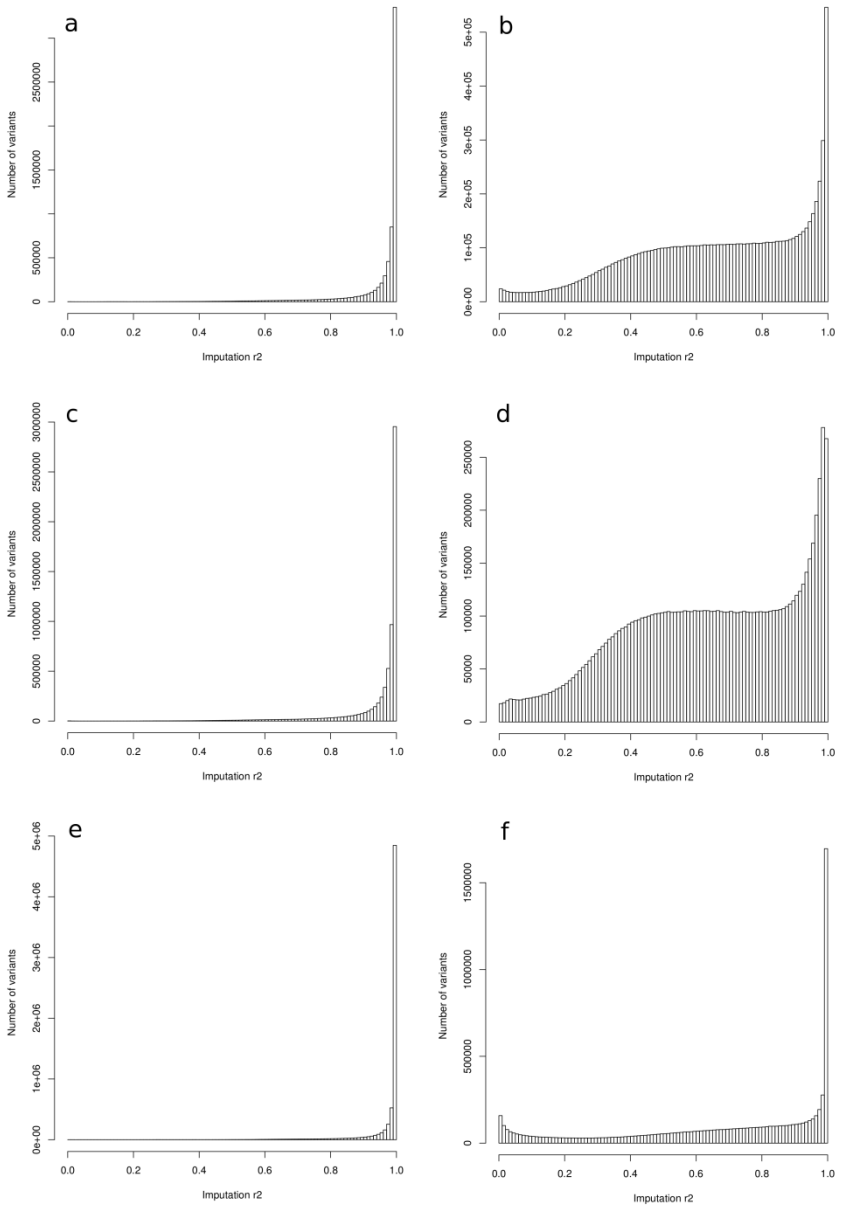
Supplementary Figures



Supplementary Figure 1

Imputation accuracy distribution.

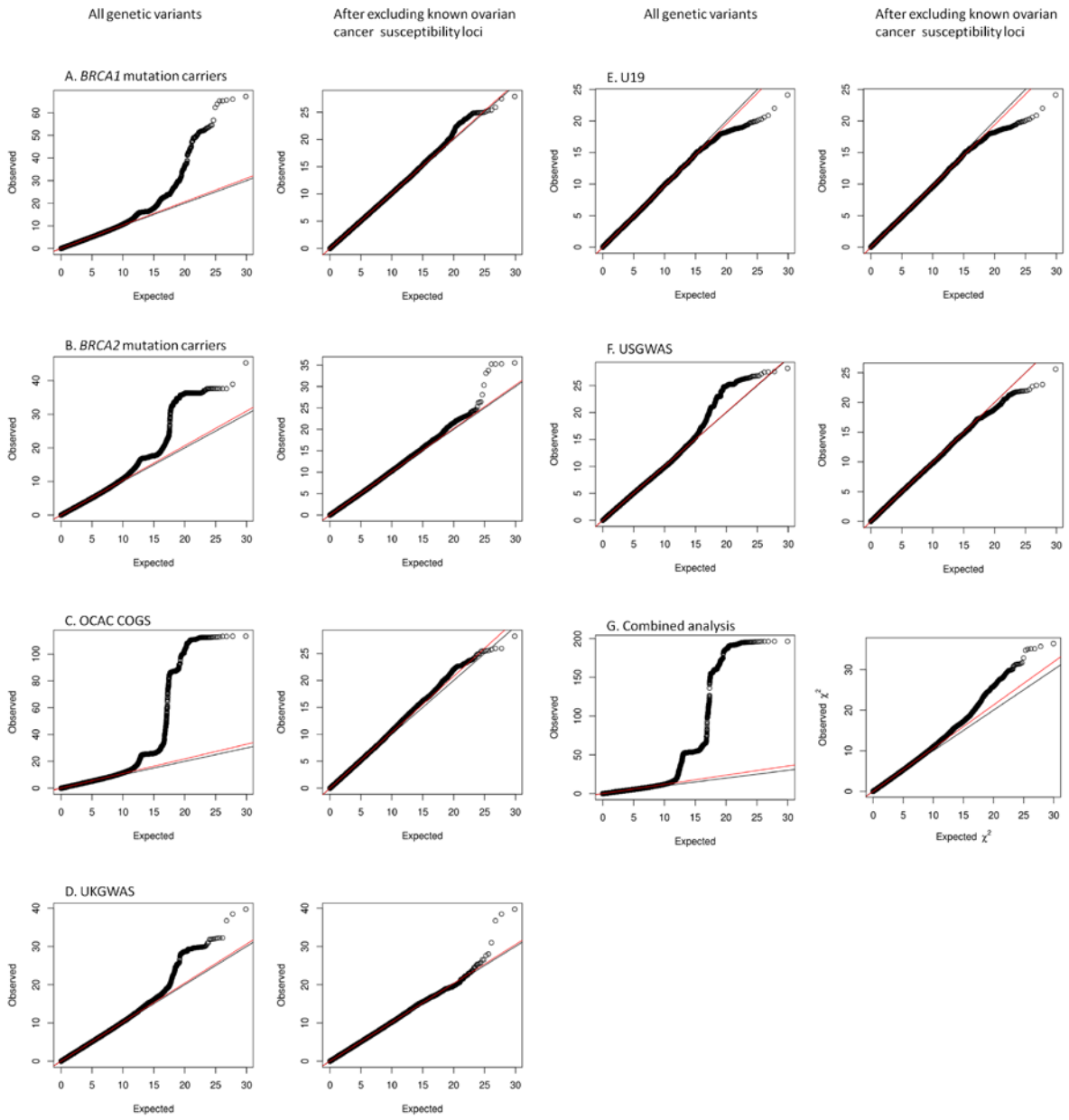
Histogram showing the distribution of imputation accuracy estimates r^2 in the first genotype imputation on the 1000 Genomes Project data v3 for SNPs with MAF >0.05 (a, c, e) and for SNPs with MAF ≤0.05 (b,d,f) in OCAC-iCOGS (a, b), *BRCA1* mutation carriers (c, d) and *BRCA2* mutation carriers (e, f).



Supplementary Figure 2

Imputation accuracy distribution.

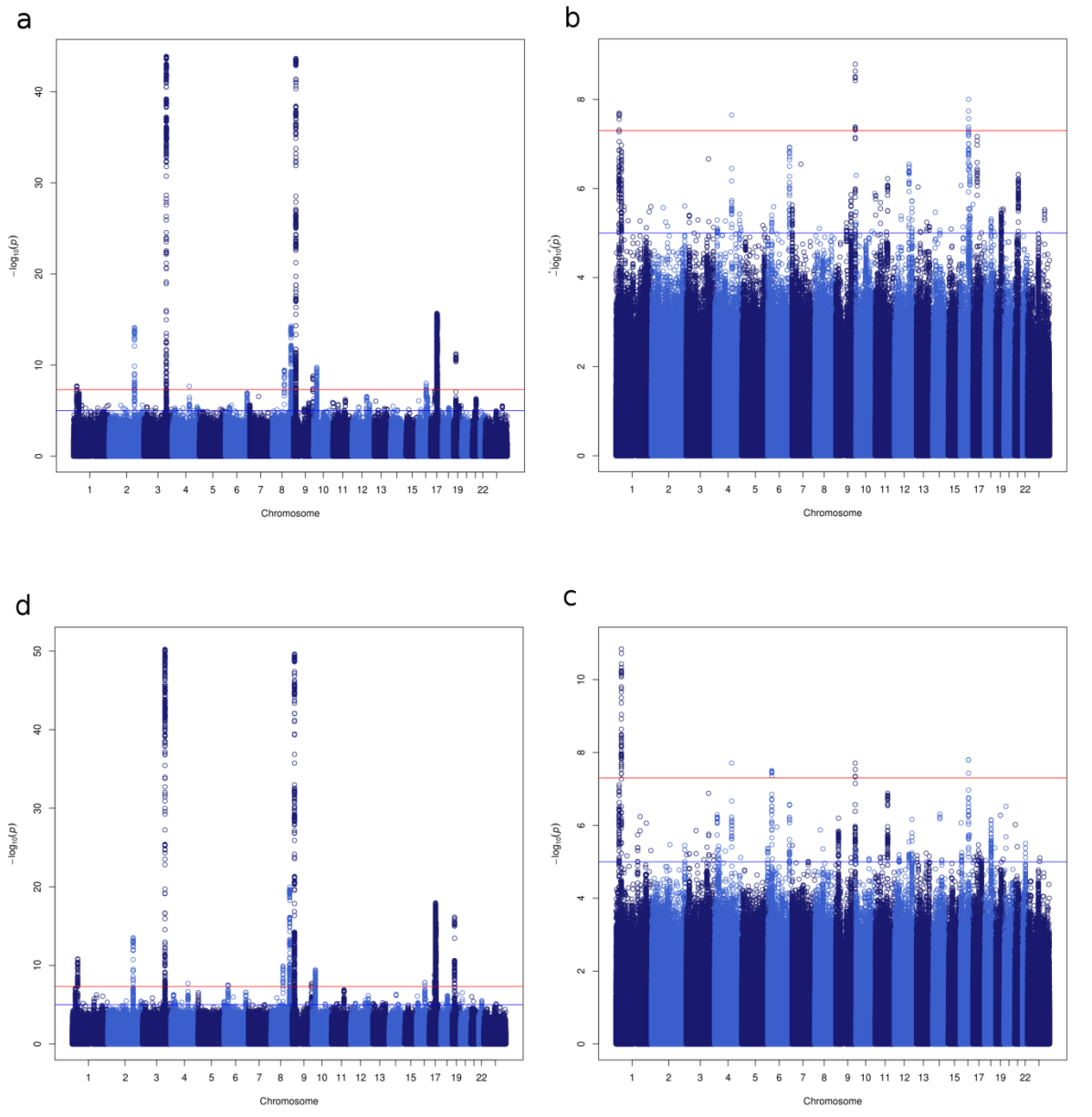
Histogram showing the distribution of imputation accuracy estimates r2 in the first genotype imputation on the 1000 Genomes Project data v3 for SNPs with MAF >0.05 (a, c, e) and for SNPs with MAF ≤0.05 (b,d,f) in the UK GWAS (a, b), the US GWAS (c, d) and the U19 GWAS (e, f).



Supplementary Figure 3

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

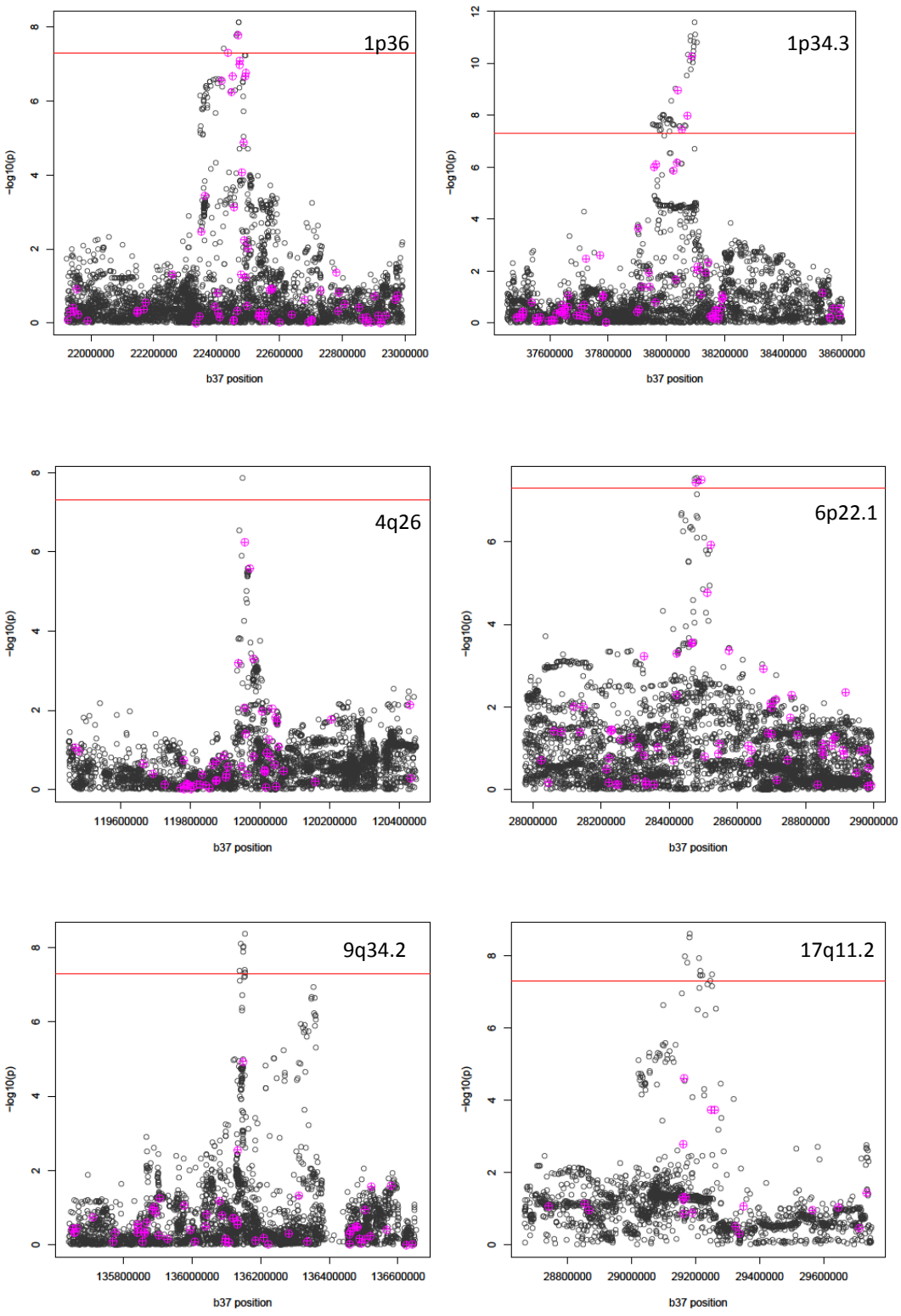
The left column on the left shows all variants and the right column shows variants not located in regions previously known to be associated with invasive ovarian cancer.



Supplementary Figure 4

Meta-analysis risk associations.

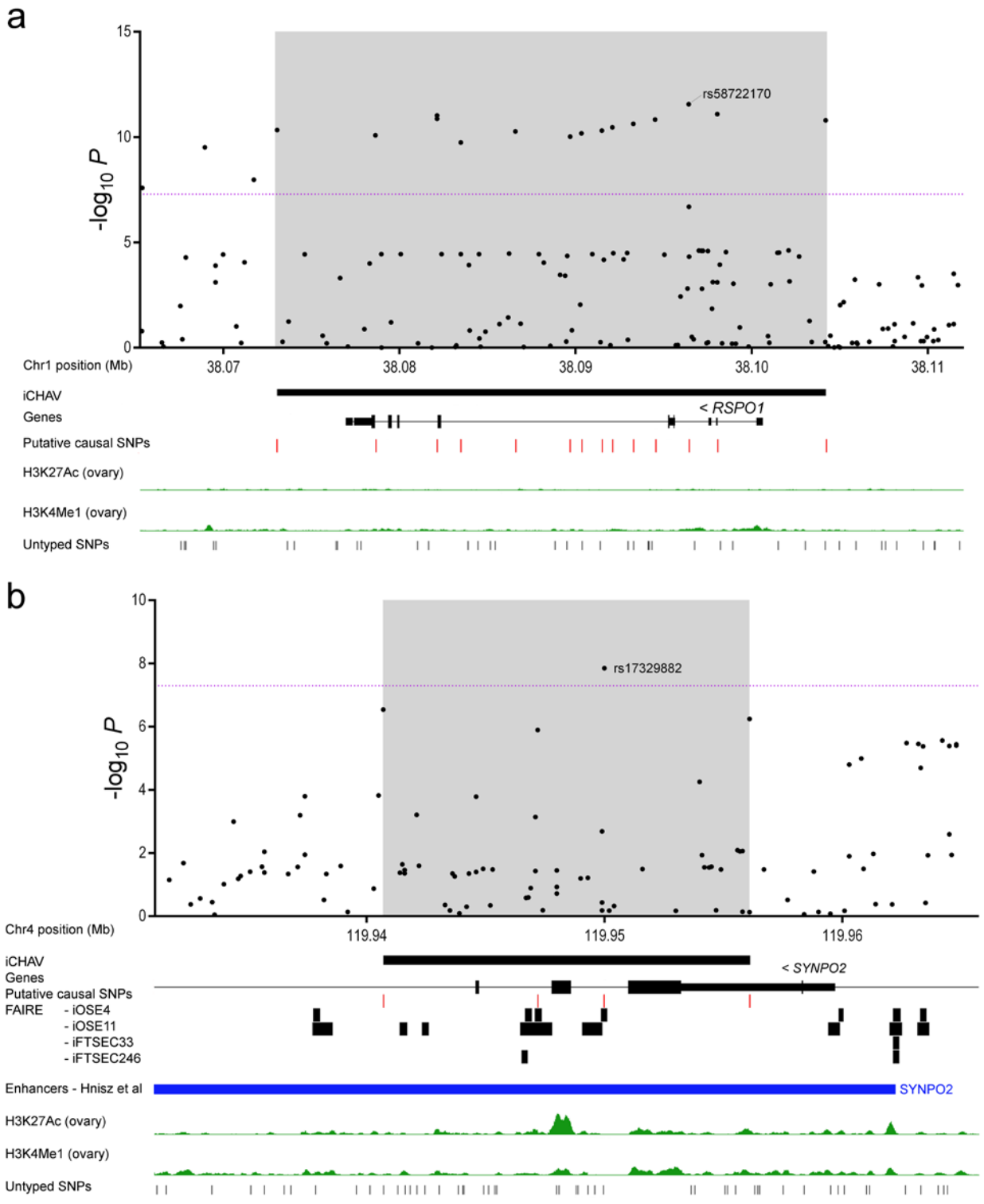
Manhattan plots showing the meta-analysis associations of genetic variants with risk of all subtypes of ovarian cancer (a, b) and serous subtype ovarian cancer (c, d) for all genetic variants available after the first imputation (a,c) and after excluding SNPs located within known ovarian cancer susceptibility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



Supplementary Figure 5.

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

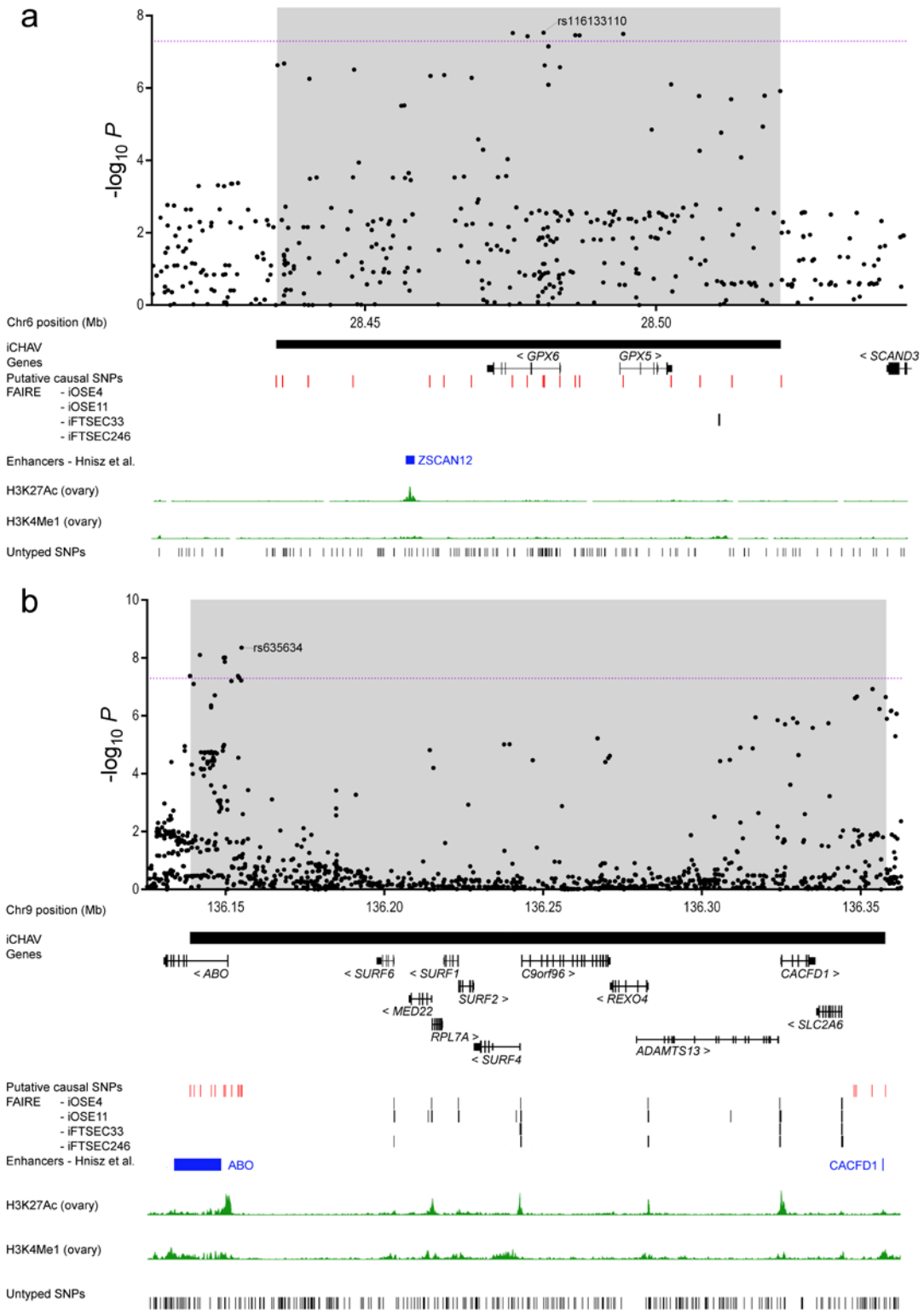
For 17q11.2 the meta-analysis was based on OCAC and BRCA2 mutation carriers only. For 1p34.3 and 6p22.1, the OCAC analysis was based on serous ovarian cancer. SNPs genotyped by the iCOGS array are shown in magenta and imputed SNPs in black.



Supplementary Figure 6

Ovarian cancer susceptibility loci at chromosome 1 and chromosome 4.

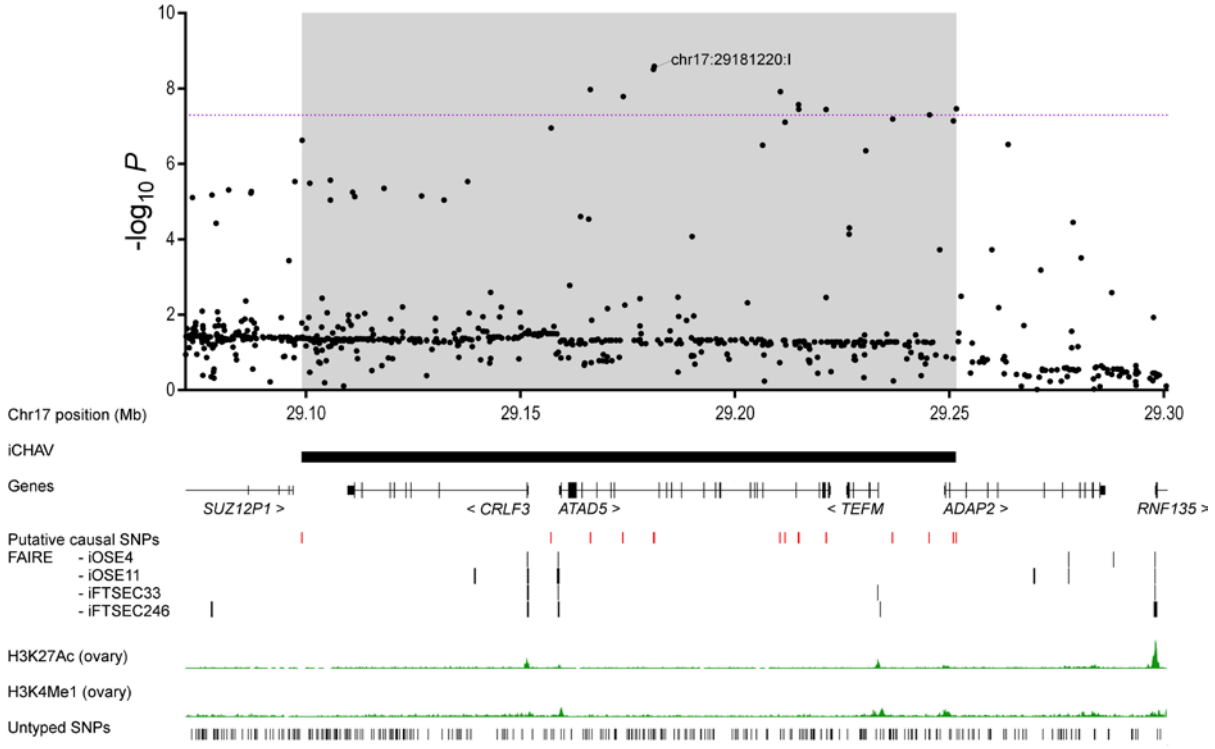
The Manhattan plot depicts the strength of association between all imputed and genotyped SNPs across the regions at chromosome 1 (a) and chromosome 4 (b). The dotted line represents the genome-wide significance level 5x10-8. FAIRE-seq data revealing potential regulatory regions in ovarian and fallopian 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[ʔ]>0.05	6,717,256	6,747,730	6,947,385	6,928,746	6,936,998	6,954,339
Imputed, MAF[ʔ]>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

ʔ 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)	1.1×10^{-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)	6.6×10^{-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	H3K4me1	Mainly OSECs/ FTSECs, some CaOV3
								CDC42		
							rs725158	promoter	H3K4me1	Only in ENCODE FAIRE
								CDC42	FAIRE, H3K27ac,	FAIRE/H3K4me1 mainly in
							rs3754496	promoter	H3K4me1	OSECs/ FTSECs
								CDC42	H3K27ac,	Only in OSECs/
							rs2268177	intron	H3K4me1	FTSECs
									H3K27ac,	
							rs10917151	Intergenic	H3K4me1	Only in OSECs
							rs2092322	Intergenic	H3K4me1	Only OSE11
								WNT4		
							rs10737462	3'UTR	H3K4me1	Only in FTE33
								WNT4	H3K27ac,	Mainly in
							rs12404660	intron	H3K4me1	OSECs/ FTSECs
								WNT4	H3K27ac,	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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