

Identification of six new susceptibility loci for invasive epithelial ovarian cancer

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 risk of EOC. After imputation to 1000 Genomes Project data, we assessed associations of 11 million genetic variants with EOC risk from 15,437 cases unselected for family history and 30,845 controls and from 15,252 *BRCA1* mutation carriers and 8,211 *BRCA2* mutation carriers (3,096 with ovarian cancer), and we 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*) variants were specifically associated with the serous EOC subtype, all with $P < 5 \times 10^{-8}$. Incorporating these variants into risk assessment tools will improve clinical risk predictions for *BRCA1* and *BRCA2* 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* (ref. 3). Furthermore, population-based GWAS have identified common variants associated with invasive EOC at 11 loci^{4–9}, but only 6 have also been evaluated in *BRCA1* and/or *BRCA2* mutation carriers. All loci analyzed 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 only¹³. However, the common genetic variants identified 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 showed 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 1000 Genomes Project data¹⁷ and evaluated the associations of these SNPs with invasive EOC risk in OCAC samples 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 to identify new 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}. For OCAC samples, genotyping data were available from 15,437 women with invasive EOC (including 9,627 with serous EOC) and 30,845 controls from the general population⁷. Imputation was performed separately for *BRCA1* mutation carriers, *BRCA2* mutation carriers, OCAC-COGS samples and samples included in the three OCAC GWAS (Supplementary Figs. 1 and 2, and Supplementary Tables 1 and 2). The meta-analysis was based on data for 11,403,952 SNPs (Supplementary Fig. 3).

Of the five EOC susceptibility loci that had 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, 7 of the 12 known EOC susceptibility loci provided evidence of association in *BRCA1* mutation carriers and 6 were associated in *BRCA2* mutation carriers. With the exception of 5p15.33 (*TERT*), all loci had hazard ratio (HR) estimates in *BRCA1* and *BRCA2* mutation carriers that were in the same direction as the odds ratio (OR) estimates for the serous subtype EOC samples in OCAC (Fig. 1). Analyzing the associations jointly in *BRCA1* and *BRCA2* mutation carriers and serous EOC cases in OCAC provided stronger evidence of association, with smaller P values for eight of the susceptibility variants in comparison to the analysis in OCAC samples alone.

Using the imputed genotypes, we observed no new associations at $P < 5 \times 10^{-8}$ in the analysis of associations in *BRCA1* and *BRCA2* mutation carriers separately. However, we identified seven previously unreported associations ($P < 5 \times 10^{-8}$) in OCAC samples alone, in the meta-analysis of EOC associations in *BRCA1* and *BRCA2* mutation carriers and OCAC samples, or in the meta-analysis in *BRCA1* and *BRCA2* mutation carriers and serous EOC cases from OCAC (Supplementary Fig. 4 and Supplementary Tables 4 and 5). SNPs in six of these loci remained genome-wide statistically significant after we reimputed genotypes with imputation parameters set to

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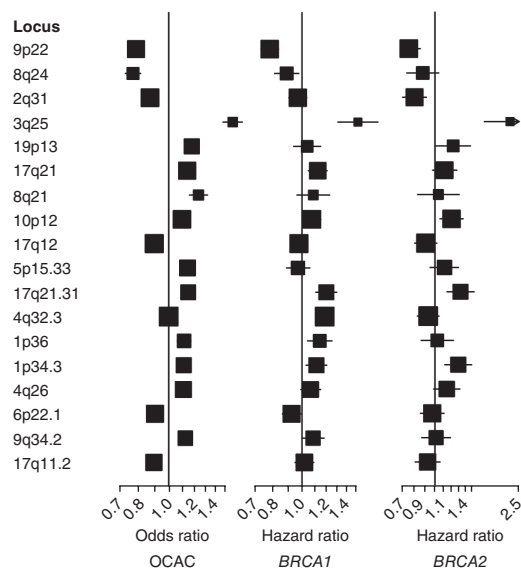


Figure 1 HR estimates for association with EOC of 12 previously reported EOC susceptibility variants and the 6 new susceptibility variants for OCAC samples, *BRCA1* mutation carriers and *BRCA2* mutation carriers. Error bars indicate 95% confidence intervals. The arrow indicates that the confidence interval extends beyond the scale of the x axis.

maximize accuracy (Fig. 1 and Table 1). We found SNPs at 17q11.2 (near *ATAD5*) to be associated with invasive EOC in the OCAC samples ($P < 5 \times 10^{-8}$) (Table 1). For the lead SNP, chr17:29181220:I, the estimated HR value for *BRCA1* mutation carriers was significantly different from the estimate in OCAC samples ($P = 0.005$); the association for *BRCA2* mutation carriers was consistent with the OCAC OR estimate (*BRCA2*-OCAC meta-analysis $P = 2.6 \times 10^{-9}$). SNPs at four loci were associated at $P < 5 \times 10^{-8}$ with risk of all invasive EOC subtypes 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 cases from OCAC ($P = 2.7 \times 10^{-12}$). In addition, SNPs at 6p22.1 were associated at a genome-wide significance level in the meta-analysis of associations with serous EOC ($P = 3.0 \times 10^{-8}$) but not in the meta-analysis of all invasive EOC associations ($P = 6.8 \times 10^{-6}$).

The most significantly associated SNP at each of the six new loci had high imputation accuracy ($r^2 \geq 0.83$). 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 $r^2 \geq 0.73$) (Supplementary Fig. 5, Supplementary Table 6 and Supplementary Note). We genotyped the leading (imputed) SNPs of the three other loci in a subset of the samples using iPLEX technology (Supplementary Note). Correlations between the expected allele dosages from imputation and the observed genotypes for the variants at 4q26 and 9q34.2 ($r^2 = 0.90$ and 0.84 , respectively) were consistent with the estimated imputation accuracy scores (0.93 and 0.83 for CIMBA samples). The lead SNP at 17q11.2 failed iPLEX design. However, the risk-associated allele was highly correlated with the AA haplotype of two genotyped variants on the iCOGS array (rs9910051 and rs3764419). This haplotype was strongly associated with ovarian cancer risk in the subset of samples genotyped using the iCOGS array (*BRCA2*-OCAC meta-analysis $P = 8.6 \times 10^{-8}$ for this haplotype and $P = 1.8 \times 10^{-8}$ for chr17:29181220:I) (Supplementary Table 7).

None of the regions contained additional SNPs that displayed EOC associations at $P < 1 \times 10^{-4}$ in OCAC samples, *BRCA1* mutation carriers or *BRCA2* mutation carriers in multi-variable analyses adjusted

Table 1 Association test results for loci associated at $P < 5 \times 10^{-8}$ in the second imputation stage

Locus	Nearest gene	rs ID	Ref ^b	Eff ^b	EAF ^h	OCAC all histologies		OCAC serous		BRCA1 mutation carriers		BRCA2 mutation carriers		Meta-analysis all histologies ^b		Meta-analysis serous ^c	
						OR (95% CI)	P	OR (95% CI)	P	r ² ^a	HR (95% CI)	P	r ² ^a	HR (95% CI)	P	P	
1p36	<i>WNT4</i>	rs56318008	C	T	0.15	0.98	1.11 (1.07–1.16)	3.9×10^{-7}	1.12 (1.07–1.18)	3.1×10^{-6}	0.98	1.15 (1.05–1.26)	1.03 (0.86–1.23)	0.74	7.6×10^{-9}	5.7×10^{-8}	
1p34.3	<i>RSP01</i>	rs58722170	G	C	0.23	0.85	1.08 (1.04–1.12)	9.7×10^{-5}	1.12 (1.08–1.18)	1.1×10^{-7}	0.83	1.14 (1.05–1.23)	1.35 (1.17–1.57)	5.2×10^{-5}	1.6×10^{-8}	2.7×10^{-12}	
4q26	<i>SYNP02</i>	rs17329882	A	C	0.24	0.95	1.09 (1.06–1.13)	5.9×10^{-7}	1.11 (1.07–1.16)	6.4×10^{-7}	0.93	1.08 (1.00–1.17)	1.15 (1.00–1.33)	0.06	1.4×10^{-8}	1.6×10^{-8}	
6p22.1	<i>GPX6</i>	rs116133110 ^e	T	C	0.31	0.99	0.93 (0.91–0.97)	9.0×10^{-5}	0.91 (0.87–0.94)	2.6×10^{-7}	0.99	0.92 (0.86–0.99)	0.97 (0.85–1.10)	0.64	6.8×10^{-6}	3.0×10^{-8}	
9q34.2	<i>ABO</i>	rs635634	C	T	0.19	0.85	1.11 (1.07–1.16)	1.1×10^{-7}	1.12 (1.08–1.18)	1.0×10^{-6}	0.83	1.11 (1.02–1.21)	1.05 (0.89–1.23)	0.55	4.4×10^{-9}	4.2×10^{-8}	
17q11.2	<i>ATAD5</i>	chr17:29181220:I ^f	A	AT	0.28	0.95	0.91 (0.88–0.94)	5.4×10^{-9}	0.91 (0.87–0.94)	8.1×10^{-7}	0.94	1.01 (0.94–1.08)	0.92 (0.80–1.05)	0.23	2.6×10^{-9d}	3.9×10^{-7d}	

Results are reported for ovarian cancer in *BRCA1* and *BRCA2* mutation carriers, for ovarian cancer as well as the serous subtype of ovarian cancer in OCAC, for the meta-analysis for ovarian cancer, and for the meta-analysis for all tumor histologies in *BRCA1* and *BRCA2* mutation carriers and serous ovarian cancer cases in OCAC. The SNP with the smallest P value is reported for each locus.

^aImputation accuracy r^2 estimate. ^b P value from the meta-analysis association test for ovarian cancer in OCAC samples and *BRCA1* and *BRCA2* mutation carriers. ^c P value from the meta-analysis association test for ovarian cancer in OCAC samples and *BRCA1* and *BRCA2* mutation carriers and serous ovarian cancer in OCAC samples. ^dMeta-analysis of ovarian cancer associations in *BRCA2* mutation carriers and OCAC samples only. ^ers116133110 is listed as rs6456822 in dbSNP. ^fchr17:29181220:I is listed as rs199661266 in dbSNP. ^gReference and effect alleles. ^hEffect allele frequency.

Table 2 Associations with ovarian cancer subtypes in OCAC samples for loci associated with ovarian cancer at $P < 5 \times 10^{-8}$ in the meta-analysis

Locus	rs ID	All histologies		Serous		Endometrioid		Clear cell		Mucinous		P_{het}^a
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	
1p36	rs56318008	1.11 (1.06–1.15)	8×10^{-7}	1.12 (1.06–1.17)	6×10^{-6}	1.09 (1.00–1.19)	0.05	1.24 (1.10–1.39)	5×10^{-4}	1.03 (0.91–1.17)	0.65	0.22
1p34.3	rs58722170	1.07 (1.03–1.11)	2×10^{-4}	1.12 (1.07–1.17)	4×10^{-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)	3×10^{-7}	1.11 (1.07–1.16)	3×10^{-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)	9×10^{-5}	0.91 (0.87–0.94)	3×10^{-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)	9×10^{-9}	1.13 (1.08–1.18)	2×10^{-7}	1.12 (1.03–1.21)	0.007	1.03 (0.92–1.16)	0.58	1.23 (1.10–1.38)	3×10^{-4}	0.23
17q11.2	chr17:29181 220:1	0.90 (0.87–0.93)	1×10^{-9}	0.90 (0.87–0.94)	2×10^{-7}	0.88 (0.82–0.95)	5×10^{-4}	0.88 (0.80–0.98)	0.020	1.01 (0.91–1.12)	0.84	0.18

^a P value for the heterogeneity in associations with different tumor subtypes.

for the lead SNP in each region, indicating that they each contain only one independent set of correlated, highly associated variants (iCHAVs). Relative to 1000 Genomes Project data, we had genotyped or imputed data covering 91% of the genetic variation at 1p36, 84% of the variation at 1p34.3 and 83% of the variation at 4q26. The other three new 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 samples for the lead SNPs at 1p34.4 and 6p22.1 but not for the lead SNPs at 1p36, 4q26, 9q34.2 and 17q11.2 (Table 2).

We carried out a competing risks association analysis in *BRCA1* and *BRCA2* mutation carriers to investigate whether these loci were 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 required actual genotypes¹⁸. The HR estimates for EOC 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 them being the causal variant; most were in non-coding DNA regions (Supplementary Table 9). None were predicted to have likely deleterious functional effects, although some were in

or near chromatin biofeatures in fallopian tube and ovarian epithelial cells, which might represent the functional regulatory targets of the risk-associated SNPs (Table 3 and 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 high-grade serous ovarian cancers (HGSOs) collected by The Cancer Genome Atlas (TCGA) indicated frequent loss or deletion at 4 risk loci (1p36, 4q26, 9q34.2 and 17q11.2) (Supplementary Table 11). Consistent with this observation, the expression of *WNT4*, *SYNPO2* and *ABO* was significantly downregulated in ovarian tumors, whereas *ATAD5* expression was upregulated ($P < 6 \times 10^{-5}$, HuEx platform). 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 tumor-eQTL associations for these genes based on data from TCGA (Supplementary Table 12). At the 1p36 locus, the most strongly associated variant, rs56318008, was located

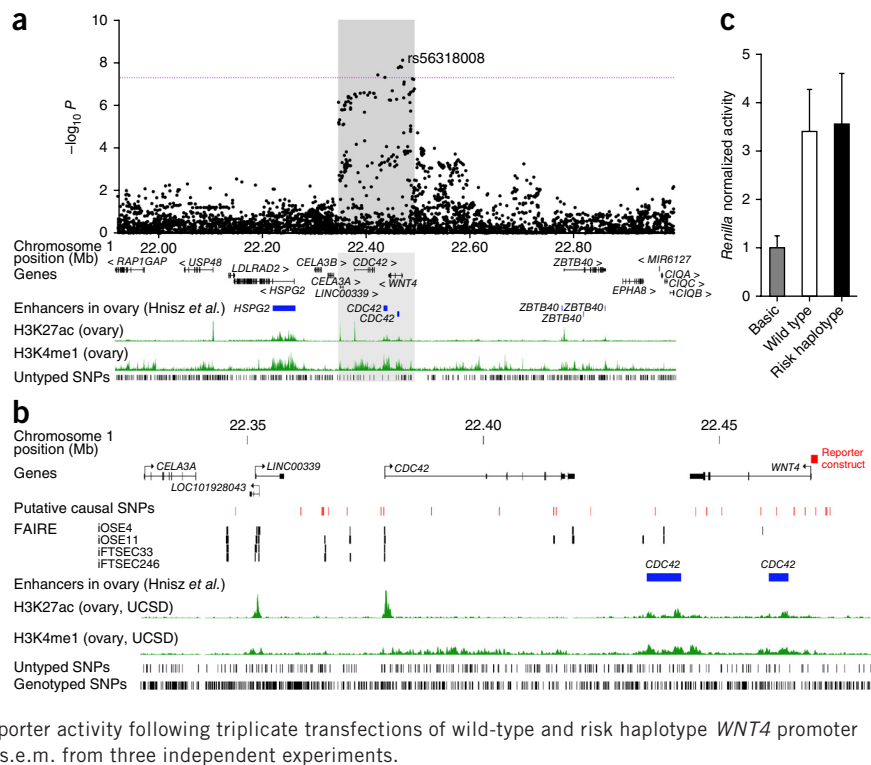
Table 3 Summary of data on SNPs, closest gene and all genes in a 1-Mb region for each locus

Loci	Position of top SNP	Number of putatively causal SNPs	Genes in window of putatively causal SNP	Number of SNPs aligned with biofeatures	Normal eQTL closest gene	Tumor DNA copy number	Significant expression difference in tumor versus normal ^c	Known role of gene in cancer	Number of genes in 1-Mb region	Other known cancer genes in 1-Mb region
1p36	Promoter region of <i>WNT4</i>	39	<i>WNT4</i> , <i>CDC42</i> , <i>LINC00339</i>	11	NS	Loss	Down	Yes	11	<i>RAP1GAP</i> , <i>CDC42</i>
1p34.3	Intron 3 of <i>RSP01</i>	15	<i>RSP01</i>	0	NS	Gain		Yes	22	<i>C1orf109</i> , <i>FHL3</i>
4q26	Intron 3 of <i>SYNPO2</i>	4	<i>SYNPO2</i>	2	NS ^b	Loss	Down	Yes	12	None
6p22.1	Intron 1 of <i>GPX6</i>	22	<i>GPX6</i> , <i>GPX5</i>	1	NA	Gain			23	<i>ZKSCAN3</i> , <i>TRIM27</i>
9q34.2	4.3 kb upstream of <i>ABO</i>	18	<i>ABO</i> , <i>SLC2A6</i> ^a	1	NS	Loss	Down	Yes	32	<i>TSC1</i> , <i>RALGDS</i> , <i>RPL7A</i> , <i>VAV2</i>
17q11.2	Intron 6 of <i>ATAD5</i>	16	<i>ATAD5</i> , <i>TEFM</i> , <i>ADAP2</i> , <i>CRLF3</i> , <i>SUZ12P1</i>	0	NS	Loss	Up	Yes	17	<i>NF1</i>

Proximal promoter regions were defined as the regions 1 kb upstream of the transcription start site. NA indicates no expression of *GPX6* in normal tissues. NS, not significant. Biofeatures are defined as open chromatin H3K4me3 or H3K27ac marks detected in normal ovarian and/or fallopian tube cells.

^aThere are 16 genes in this region—*ABO*, *SURF6*, *MED22*, *RPL7A*, *SNORD24*, *SNORD36B*, *SNORD36A*, *SNORD36C*, *SURF1*, *SURF2*, *SURF4*, *C9orf96*, *REXO4*, *ADAMTS13*, *CACFD1* and *SLC2A6*; however, all SNPs are within or upstream of *ABO* or upstream of *SLC2A6*. ^bTrend $P = 0.067$. ^c $P < 6 \times 10^{-5}$ with the HuEx platform.

Figure 2 The 1p36 EOC susceptibility locus. (a) The Manhattan plot depicts the strength of association between all imputed and genotyped SNPs across the region bound by hg19 coordinates chr. 1: 21,922,893–22,991,643. The dotted line represents the genome-wide significance level of 5×10^{-8} . Additional tracks show genes and enhancers in the ovary as described in Hnisz *et al.*³⁸. Positions of SNPs for which imputation $r^2 < 0.3$ and/or minor allele frequency (MAF) < 0.005 are shown in the bottom track as 'untyped' SNPs. H3K27ac, acetylation of histone H3 at lysine 27; H3K4me1, monomethylation of histone H3 at lysine 4. (b) The shaded iCHAV region 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 formaldehyde-assisted regulatory element sequencing (FAIRE-seq) data derived from ovarian cells are represented by black marks, and the locations of predicted *CDC42* enhancers³⁸ are represented by blue boxes. The positions of genotyped SNPs and those that were neither genotyped nor well imputed ('untyped') are shown. (c) Normalized luciferase reporter activity following triplicate transfections of wild-type and risk haplotype *WNT4* promoter constructs in iOSE4 cells. Error bars represent the s.e.m. from three independent experiments.



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 were located in *CDC42* and *LINC00339*, and several were in putative regulatory domains in ovarian tissues (Fig. 2 and Supplementary Table 10). *CDC42* is known to have a role in migration and signaling in ovarian and breast cancers^{19,20}. SNPs at 1p36 are also associated with increased risk of endometriosis, and *WNT4*, *CDC42* and *LINC00339* have all been implicated in endometriosis²¹, a known risk factor for endometrioid and clear cell EOCs²².

The strongest associated variant at 1q34, rs58722170, was 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 it regulates *WNT4* expression in the ovaries²⁵. *SYNPO2* at 4q26 encodes myopodin, which is involved in cell motility and growth²⁶ and has a reported tumor-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 group³³. The moderate correlation between rs635634 and rs505922 and the considerably weaker EOC association of rs505922 ($P = 1.2 \times 10^{-5}$) suggest that the association with blood group is probably not driving the risk association. The indel chr17:29181220:I at 17q11.2 is located in *ATAD5*, which acts as a tumor-suppressor gene^{34–36} (Supplementary Fig. 8). *ATAD5* protein modulates the interaction between *RAD9A* and *BCL2* to induce DNA damage-related apoptosis. Finally, rs116133110, at 6p22.1, lies in *GPX6*, which has no known role in cancer.

The 6 new 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 loci explain approximately 3.9% of the excess familial relative risk of EOC in the general population and account for approximately 5.2% of the polygenic modifying variance for EOC in *BRCA1* mutation carriers and 9.3% of the variance in *BRCA2* mutation carriers. The similarity in the magnitude of the associations between *BRCA1* and *BRCA2* mutation carriers and cases from 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 EOC³⁷. This model predicts large differences in absolute EOC risk between individuals carrying many risk-associated alleles and individuals carrying few alleles for EOC susceptibility in *BRCA1* and *BRCA2* mutation carriers^{13,16}. Incorporating EOC susceptibility variants into risk assessment tools will improve risk prediction and might be particularly useful for *BRCA1* and *BRCA2* mutation carriers.

URLs. Nature Publishing Group, *Nature Genetics*–iCOGS, <http://www.nature.com/icogs/>; The Cancer Genome Atlas (TCGA) Project, <http://cancergenome.nih.gov/>; cBio Cancer Genomics Portal, <http://www.cbioportal.org/>; Pupasuite 3.1, <http://pupasuite.bioinfo.cipf.es/>; CIMBA quality control guidelines, <http://ccge.medschl.cam.ac.uk/consortia/cimba/members/data%20management/CIMBA%20and%20BCAC%20Quality%20Control%20November%202008%20v2.doc>; R software, <http://www.r-project.org/>.

METHODS

Methods and any associated references are available in the online version of the paper.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

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COMPETING FINANCIAL INTERESTS

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ONLINE 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 clinics¹⁵, 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 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 15,437 women diagnosed with invasive 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 imputation for 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 Sequenom'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 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* mutation carriers, *BRCA2* mutation carriers, the three OCAC GWAS and the 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 of <95%, if they showed low or high heterozygosity, if they were not female or had ambiguous sex or if they were duplicates (cryptic or intended). In the 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 a call rate of < 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 association $P < 1 \times 10^{-5}$ from each of the newly identified loci. We used the R GenABEL library version 1.6.7 for quality control.

Genotype data were available for analysis from iCOGS for 199,526 SNPs in OCAC-iCOGS samples, 200,720 SNPs in *BRCA1* mutation carriers and 200,908 SNPs in *BRCA2* mutation carriers. After quality control, 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* mutation carriers, *BRCA2* mutation carriers, OCAC-iCOGS samples and each of the OCAC GWAS. We imputed variants from 1000 Genomes Project data using the v3 April 2012 release¹⁷ as the reference panel. For OCAC-iCOGS samples, 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 step. We carried out pre-phasing using SHAPEIT software⁴⁰. We used IMPUTE version 2 software for the subsequent imputation⁴¹ for all studies with the exception of the US GWAS, for which the MACH algorithm implemented in Minimac software version 2012.8.15, MACH version 1.0.18, was used. To perform imputation, we divided the data into segments of approximately 5 Mb each. We excluded SNPs from the association analysis if their imputation accuracy was $r^2 < 0.3$, their MAF was <0.005 in *BRCA1* or *BRCA2* mutation carriers or their accuracy was $r^2 < 0.25$ in OCAC-iCOGS samples, the UK GWAS, the US GWAS or the Mayo GWAS.

We performed more accurate imputation for the regions around the new EOC loci from the joint analysis of the data from *BRCA1* and *BRCA2* mutation carriers and the general population (any SNP with association $P < 5 \times 10^{-8}$). The boundaries of these regions were set 500 kb away from any significantly associated SNP in the region. As in the first run, 1000 Genomes Project data v3 were used as the reference panel, and IMPUTE2 software was applied. However, for the second round of imputation, we imputed genotypes without pre-phasing to improve accuracy. To further increase imputation accuracy, we changed some of the default parameters in the imputation procedure. These included an increase in the MCMC iterations to 90 (out of which the first 15 were used as burn-in), an increase in the buffer region to 500 kb and an increase in 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 SNP associations with serous ovarian cancer after excluding all cases with any other or unknown tumor 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 samples and the three GWAS and pooled data thereafter using a fixed-effects meta-analysis. We carried out the analysis of reimputed genotypes for putative new susceptibility loci jointly for the OCAC-iCOGS samples and the 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 to the age at last observation. Breast cancer diagnosis was not considered to be a censoring event. To account for the non-random sampling of *BRCA1* and *BRCA2* mutation carriers with respect to their disease status, we conducted the analyses by modeling the retrospective likelihood of the observed genotypes conditional on the disease phenotype¹⁸. We assessed the associations between genotype and risk of ovarian cancer using the 1-degree-of-freedom score test statistic based on retrospective likelihood^{18,42}. 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 score⁴³. 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 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 (ref. 44).

We evaluated whether there was 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* mutation carriers, *BRCA2* mutation carriers and OCAC samples.

For one of the new 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 this analysis was therefore restricted to 14,733 ovarian cancer cases and 9,165 controls from OCAC-COGS and 8,185 *BRCA2* mutation carriers for whom genotypes were available for both variants based on iCOGS. The association between the AA haplotype and risk was tested using logistic regression in OCAC samples and using Cox regression in *BRCA2* mutation carriers.

Meta-analysis. We conducted a meta-analysis of the EOC associations in *BRCA1* mutation carriers, *BRCA2* mutation 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 HR estimate for the association with EOC risk in *BRCA1* and *BRCA2* mutation carriers and the logarithm of the per-allele OR estimate for the association with disease status in OCAC. For associations in *BRCA1* and *BRCA2* carriers, we used the kinship-adjusted variance estimator⁴³, which allows for the 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* mutation carriers, *BRCA2* mutation carriers and EOC samples in OCAC, irrespective of tumor histological subtype, and a second using only the associations with serous EOC in OCAC samples. The number of *BRCA1* and *BRCA2* mutation carriers with tumor 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^{45–49}. Meta-analyses were carried out using Meta software, 2011-03-25 release⁵⁰.

Candidate causal SNPs in each susceptibility region. 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 likelihood of the most strongly associated SNPs⁵¹. The remaining variants were then analyzed using Pupasuite 3.1 to identify potentially functional variants^{52,53} (**Supplementary Table 9**).

Functional analysis. *Expression quantitative trait locus analysis in normal ovarian and fallopian tube cells.* Early-passage primary normal ovarian surface epithelial cells (OSECs) and fallopian tube epithelial cells were collected 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-CM⁵⁴. Fallopian tube epithelial cells were collected by Pronase digestion as previously described⁵⁵, plated onto collagen-coated plastics (Sigma) and cultured in DMEM/F12 (Sigma-Aldrich) supplemented with 2% Ultrosor G (BioSeptra) and 1× penicillin-streptomycin (Lonza). By the time of RNA isolation, the 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*. Cell lines were routinely tested for mycoplasma.

For gene expression analysis, RNA was isolated from 59 early-passage samples: 54 OSECs and 5 FTSECs from cell cultures collected at ~80% confluency using the Qiagen miRNAeasy kit with on-column DNase I digestion. RNA (500 ng) was reverse transcribed using the Superscript III kit (Life Technologies). We preamplified 10 ng of cDNA using TaqMan Preamp Mastermix; the resulting product was diluted 1:60 and used to quantify gene expression with 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 $\Delta\Delta C_t$ 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, rs050922 at 9q34.2 and rs3764419 at 17q11.2. Correlations between genotype and gene expression were calculated in R. Genotype-specific gene expression in normal tissue cell lines (eQTL analysis) was compared using the Jonckheere-Terpstra test. Data were normalized to the four control genes, and we tested for eQTL associations, grouping OSECs and FTSECs together. Second, OSECs were analyzed alone. eQTL analyses were performed using three genotype groups or two groups (with the rare homozygote samples grouped together with the heterozygote samples).

eQTL analysis in primary ovarian tumors. eQTL analysis in primary tumors was based on publicly available data from the TCGA Project, which included 489 primary HGSOCs. The methods have been described elsewhere⁵⁶. Briefly, we determined the ancestry for each case on the basis of germline genotype data using EIGENSTRAT software with 415 HapMap genotype profiles as a control set. Only populations of northern and western European ancestry 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 500 kb on either side of the variant) were evaluated using a linear regression model with the effects of somatic copy number and CpG methylation being deducted. (For miRNA expression, the effect of CpG methylation was not adjusted for because these data were not available.) To correct for multiple tests, we adjusted the test *P* values using the Benjamini-Hochberg method. A significant association was defined by a false discovery rate (FDR) of <0.1.

Having established genome-wide *cis*-eQTL associations in this series of tumors, 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 on the basis of the Affymetrix 6.0 array. Using these genotypes and the IMPUTE2 March 2012 1000 Genomes Project 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 samples⁵⁷. 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 were defined by an FDR of <0.1.

Regulatory profiling of normal ovarian cancer precursor tissues. We performed genome-wide FAIRE and chromatin immunoprecipitation with sequencing (ChIP-seq) for H3K27ac and H3K4me in two normal OSECs, two normal FTSECs and two HGSOC cell lines (UWB1.289 and CAO3) (S.C., H.S., D.H., K.L. and K.B.K. *et al.*, unpublished data). Cell lines were routinely tested for mycoplasma. These data sets annotate the epigenetic signatures of open chromatin and collectively indicate transcriptional enhancer regions. We analyzed the FAIRE-seq and ChIP-seq data sets and publically available genomic data on promoter and UTR domains, intron-exon boundaries and the positions of noncoding RNA transcripts to identify SNPs from the 100:1 likely causal set that aligned with biofeatures that might provide evidence of SNP functionality.

Candidate gene analysis using genome-wide profiling of primary ovarian cancers. **Data sets: the TCGA Project and COSMIC data sets.** TCGA has performed extensive genomic analysis of tumors from a large number of tissue types, including almost 500 high-grade serous ovarian tumors. These data include somatic mutations, DNA copy number, mRNA and miRNA expression, and DNA methylation. COSMIC is the catalog of somatic mutations in cancer that collates information on mutations in tumors from the published literature⁵⁸. 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 tumors.

Somatic coding sequence mutations. We analyzed 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 COSMIC⁵⁸ and whether the gene was a known cancer gene in the Sanger Cancer Gene Census.

mRNA expression in tumor and normal tissue. Normalized and gene expression values (level 3) from gene expression profiling data were obtained from the TCGA data portal for three different platforms (Agilent, Affymetrix HuEx and Affymetrix U133A). We analyzed only the 489 primary serous ovarian tumor samples included in the final clustering analysis⁵⁷ and 8 normal fallopian tube samples. The boxplot function in R was used to compare ovarian tumor samples to the fallopian tube samples for 91 coding genes with expression data on any platform within a 1-Mb region around the most significant SNP at the 6 loci. A difference in relative expression between EOC samples and normal tissue was analyzed using the Wilcoxon rank-sum test.

DNA copy number analysis. Serous EOC samples for 481 tumors with log₂ copy number data were analyzed using the cBio Portal for the analysis of TCGA data^{59,60}. 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. At a region, the frequency of gain and amplification were combined as 'gain', and homozygous deletion and heterozygous loss were combined as 'loss'.

Analysis of copy number versus mRNA expression. Serous EOC samples for 316 complete tumors (those with CNA, mRNA and sequencing data) were analyzed. Graphs were generated using the cBio Portal for the analysis of TCGA data, and the settings were mRNA expression data z score (all genes) with a z-score threshold of 2 (default setting) and putative CNAs (GISTIC). The z score was the number of s.d. 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 assays. The putative causal SNPs at the 1p36 locus lie in the *WNT4* promoter, and we therefore 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 coordinates chr. 1: 22,469,416–22,470,869 were generated by Custom Gene Synthesis (GenScript) and then subcloned into pGL3-basic (Promega). Equimolar amounts of luciferase constructs (800 ng) and pRL-TK *Renilla* (50 ng) were cotransfected into $\sim 8 \times 10^4$ iOSE4 (ref. 61) 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 h after transfection using a BioTek Synergy H4 plate reader. Statistical significance was tested by log transforming the data and performing two-way ANOVA, followed by Dunnett's multiple-comparisons test in GraphPad Prism. The iOSE4 cell line (derived by K. Lawrenson) was maintained under standard conditions; it was routinely tested for mycoplasma and underwent short tandem repeat profiling.

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