Supplementary Note, Tables and Figures

Common variants at 19p13 are associated with susceptibility to ovarian cancer

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Supplementary Note

Quality Control Procedures

For phase 1, SNPs were excluded if (i) they deviated from Hardy-Weinberg equilibrium (HWE) at $P < 10^{-4}$, (ii) they had a MAF < 1 percent, (iii) MAF was between 1 percent and 5 percent and call rate < 99 percent and (iv) MAF > 5 percent and call rate < 95 percent. In phase 1, 507,094 out of 540,573 SNPs (94 percent) passed QC. Quantile-quantile (Q-Q) plots of the distribution of test statistics to compare genotype frequencies in cases versus controls in the phase 1 EOC susceptibility GWAS suggested there was little evidence of any general inflation of the test statistics (estimated inflation factor $\lambda = 1.055$, $\lambda_{1000} = 1.026$ based on the bottom 90 percent of the distribution). We excluded SNPs for the phase 2 data if the sum of the test statistics for deviation from HWE for the ten studies was significant at $P < 10^{-5}$ or if the SNPs had a call rate of <95 percent or if the MAF < 0.05. A total of 4,649 out of 4,715 (98.6 percent) survival-selected SNPs passed QC criteria in phase 2 and the mean SNP call rate was 99.6 percent.

We used only samples with called genotypes on at least 80 percent of SNPs. Nineteen samples were included as duplicates in phase 1 and genotype concordance rate for these pairs was 99.99 percent. One hundred and twenty-two samples were included as duplicates in phase 2 and duplicate concordance rate was 99.99 percent. In phase 1, 73 cases (4 percent) failed genotyping quality control and were excluded; among the 1,768 eligible cases, 99.5 percent of cases and 100 percent of controls had call rates >95 percent. In phase 2, 131 cases (3.1 percent) and 142 controls (2.9 percent) failed genotyping quality control criteria. Among the eligible phase 2 subjects, 100 percent of cases and controls had call rates>95 percent.

For the four studies included in phase 3 (TOR, NCO, MAY, MOF) where genotype data were available from an independent GWAS, samples were excluded if the call rate was <95 percent, if duplicate concordance was <100 percent or if Caucasian ancestry was <80 percent. SNPs were excluded if the call rate was <95 percent or if a test for HWE yielded $P<10^{-4}$.

We used the following criteria as a measure of acceptable genotyping for Taqman and iPlex genotyping of phase 3 studies: (i) > 2 percent sample duplicates included; (ii) concordance rate for the duplicates greater than or equal to 98 percent; (iii) overall call rate (by study) > 95 percent; (iv) call rates > 90 percent for each individual 384-well plate and (v) no deviation from HWE in controls (P > = 0.05). We also excluded samples genotyped by iPlex with call rates <80 percent – other SNPs also genotyped in the same assay (3.3 percent of cases and 3.5 percent of controls). Of the remaining samples, 95 percent of cases and 97 percent of controls had call rates of >95 percent. Genotyping consistency across laboratories was also evaluated by genotyping a common panel of CEPH (Centre d'Etude du Polymorphisme Humain)-Utah trios including 90 individual DNA samples, 5 duplicate samples and 1 negative control. The concordance of genotyping results between the centers was required to be greater than 98 percent in order for the genotype data to be included. Three studies (NCO, SOC+UKO and HOC) showed HWE P-values of <0.05 among controls and one case-only study (LAX) showed HWE P-values of <0.05 among cases (Supplementary table 6). Genotype clustering was reviewed for these studies and was good. We therefore retained these data in the analysis. For Taqman genotyping of rs2363956, the PVD study had a call rate of 92 percent. The exclusion of this case-only study did not impact the survival results of the

phase 3 analysis and so was retained. The YAL study showed genotyping call rates of <90 percent and was excluded from the final analysis. The remaining studies met the above criteria.

Supplementary table 1: Characteristics of cases by phase.

	Phase 1	Phase 2	Phase 3	Total
Total no. subjects with survival time data	1,512	3,363	4,076	8,951
Median time at risk (years)	2.6	2.8	2.1	2.4
Median time from diagnosis to study entry (years)	2.6	0.3	0.2	0.2
No. of deaths before 5 years post diagnosis	397	1,472	1,489	3,358
Median age at diagnosis, y	58	58	59	59
Histopathologic type (%)				
Serous	50.7	60.5	61.3	59.2
Mucinous	10.1	6.2	4.8	6.3
Endometrioid	17.7	13.6	11.1	13.2
Clear Cell	9.2	6.2	7.0	7.1
Mixed Cell	1.9	4.3	2.9	3.3
Other Specified Epithelial	0.5	3.8	6.3	4.4
Undifferentiated	0.8	0.2	4.0	2.0
Unspecified Epithelial	9.1	5.3	2.6	4.7
Clinical Stage (%)				
Low (I,II)	41.7	30.6	24.0	29.6
High (III,IV)	35.8	59.3	70.3	60.1
Unknown	22.5	10.1	5.7	10.3
Grade (%)				
Well differentiated	13.4	11.3	8.4	10.4
Moderately differentiated	23.5	21.0	21.9	21.9
Poorly/undifferentiated	38.6	47.6	62.9	52.9
Unknown	24.4	20.1	6.8	14.9

Supplementary table 2: Description of studies contributing to phases 1, 2 and 3.

Study Name	Study abbrev.	Study population	Study type	Survival Time	Number of Subjects[1]	
					cases (surv[2])	controls
STAGE1						
SEARCH Cambridge UK	SEA	UK	Population based	Cancer registry	1089 (940)	-
UKOPS (United Kingdom Ovarian Cancer Population Study)	UKO	UK	Population based	Cancer registry	500 (450)	-
Cancer Research UK Familial Ovarian Cancer Register	FOCR	UK	Familial cancer register	Personal reports	32 (24)	-
Royal Marsden Hospital study	RMH	UK	Hospital based	Medical records	147 (98)	-
UK 58 Birth cohort	58 BC	UK	Cohort		-	1436
UK Colorectal control	NSCR	UK	Population based		-	917
Subtotal					**1768 (1512)**	**2353**
STAGE 2						
Australian Cancer Study (ovarian cancer); Australian Ovarian Cancer Study	AUS	Australia	Population based	Medical records	1024(981)	1,099
Diseases of the Ovary and their Evaluation Study	DOVE	Washington State, USA	Population based	Cancer registry	700 (700)	727
Polish Ovarian Cancer Study (1)	POL1	Poland	Population based	Cancer registry	518 (229)	507
Los Angeles County Case-Control Studies of Ovarian Cancer	USC	Los Angeles, USA	Population based	Cancer registry	269 (269)	352
Malignant Ovarian Cancer study	MAL	Copenhagen, Denmark	Population based	Cancer registry	444 (444)	551
Gilda Radner familial ovarian cancer register	GR	Buffalo, USA	Familial cancer register	Medical records, tumor registry	112 (11)	-
Hormones and ovarian cancer prediction study	HOP	Pittsburgh, USA	Population based		356	372
Genetic Epidemiology of Ovarian Cancer	STA	Stanford, USA	Population based	Cancer registry	234 (233)	330
UKOPS (United Kingdom Ovarian Cancer Population Study)	UKO	UK	Population based	Cancer registry	170(144)	450
SEARCH Cambridge UK	SEA	UK	Population based	Cancer registry	29 (28)	-
Polish Ovarian Cancer Study (2)	POL2	Warsaw & Lodz, Poland	Population based	Cancer registry	237 (217)	228
Bavarian ovarian cancer study	BAV	Germany	Population based	Cancer registry	145 (107)	194
Subtotal					**4238 (3363)**	**4810**
STAGE 3						
Moffitt Ovarian Cancer Study	MOF	Tampa, USA	Population based	National death index and death certificates	267 (234)	181
UC Irvine Ovarian Cancer Study, California	UCI	California, USA	Population based	Cancer registry	158 (154)	198

Mayo Clinic Ovarian Canver Study	MAY	Upper Midwest, USA	Clinic based	National death index, social security and medical records	361 (352)	520
North Carolina Ovarian Cancer Study	NCO	North Carolina, USA	Population based	National death index	495 (495)	655
Hawaii Ovarian Cancer Study	HAW	Hawaii, USA	Population based	Cancer registry	81 (80)	161
Hannover-Minsk Ovarian Cancer Study	HMO	Germany	Hospital based	Medical records	195	335
Hannover-Jena Ovarian Cancer Study	HJO	Germany	Hospital based	Medical records	223(212)	591
Familial ovarian tumour study	TOR	Canada	Population based		724	556
German Ovarian Cancer Study	GER	Germany	Population based	Population registry	187 (187)	398
Ovarian Cancer Study	OVA	Canada	Population based		455	437
Netherlands Ovarian Cancer Study	NTH	Netherlands	Population based	Population registry	245 (105)	577
Southhampton Ovarian Cancer Study	SOC	UK	Population based	Cancer registry	301 (85)	-
UKOPS (United Kingdom Ovarian Cancer Population Study)	UKO	UK	Population based	Cancer registry	61 (49)	384
Helsinki Ovarian Cancer Study	HOC	Finland	Population based		248	454
Belgium Ovarian Cancer Study	BEL	Belgium	Hospital based	Medical records	173 (105)	432
Brighman Women's Hospital Study	BWH	Boston, USA	Hospital based		133	142
deCODE[3]	DEC	Iceland	Population based	Cancer registry	194 (194)	
Gilda Radner Hereditary Cancer Program[4]	LAX	Los Angeles, USA	Hospital based	Medical records	(279)	-
Pelvic Mass Study[4]	PVD	Copenhagen, Denmark	Hospital based	Cancer registry	(199)	-
The Cancer Genome Atlas[4]	TCG	USA	Hospital based	Medical records	(327)	-
Scottish Randomised Trial in Ovarian Cancer [4]	SCO	UK	Hospital based	Clinical Trial	(837)	-
Hormones and ovarian cancer prediction study[4]	HOP	Pittsburgh, USA	Population based	Medical records, tumor registry	(182)	-
Subtotal					**4501(4076)**	**6021**
TOTAL					**10507 (8951)**	**13184**

[1]Totals represent the number of non-Hispanic White Europeans passing genotyping quality control criteria.

[2]Number of cases included in survival analyses.

[3]Only effect estimates were available based on the analysis of 194 EOC cases and 32,900 controls

[4]Studies were only included in survival analysis.

Supplementary table 3: Allele frequencies of rs2363956 and rs8170 in cases and controls by study.

	rs2363956 (*t* allele)		rs8170 (*t* allele)	
Study Name	Cases	Controls	Cases	Controls
Phase 1	0.51	0.50	0.20	0.18
Phase 2				
AUS	0.50	0.49	0.20	0.19
BAV	0.53	0.48	0.22	0.18
DOV	0.50	0.47	0.21	0.19
GR+HOP	0.50	0.51	0.19	0.17
MAL	0.51	0.52	0.22	0.21
POL1	0.52	0.47	0.22	0.19
POL2	0.52	0.51	0.22	0.22
SEA+UKO	0.52	0.48	0.21	0.17
STA	0.55	0.48	0.24	0.16
USC	0.51	0.50	0.24	0.21
Phase 3				
BEL	0.53	0.52	0.24	0.20
BWH	0.50	0.50	0.20	0.21
GER	0.51	0.51	0.21	0.20
HAW	0.48	0.53	0.18	0.22
HJO	0.49	0.50	0.19	0.20
HMO	0.51	0.48	0.28	0.24
HOC	0.44	0.41	0.22	0.22
MAY	0.54	0.48	0.19	0.18
MOF	0.52	0.51	0.21	0.21
NCO	0.52	0.49	0.18	0.20
NTH	0.50	0.47	0.22	0.19
OVA	0.53	0.50	0.21	0.19
SOC+UKO	0.53	0.49	0.20	0.19
TOR	0.52	0.46	0.20	0.17
UCI	0.56	0.47	0.22	0.19

Supplementary table 4: Ovarian cancer cell lines, their clinical characteristics and culture conditions used for candidate gene expression analysis.

Cell Line Name	Clinical description of primary ovarian tumor	Tissue culture medium
1847	Epithelial 'like'	RPMI 1640 +10% FBS + L-Glu
TOV 112D	Endometrioid	M199:MCDB105 + 15% FBS+ L-Glu
1847 AD	None given	RPMI 1640 +10% FBS + L-Glu
TOV 21G	Clear cell	M199:MCDB105 + 15% FBS+ L-Glu
CaOv3	Adenocarcinoma	DMEM + 10% FBS + NEAA/glucose
Cov318	Serous	DMEM +10% FCS+Lglu+Lasparagine
Cov 644	Mucinous	DMEM +10% FCS+Lglu+Lasparagine
EFO 27	mucinous papilary adenocarcinoma	RPMI 1640 + 20% FBS + L-Glu + NEAA + Na Pyr
Hey A8	moderately differentiated papillary cystadenocarcinoma	RPMI 1640 +10% FBS
Hoc 7	Well differentiated serous from ascites	DMEM + 10%FBS
Igrov 1	Untreated adenocarcinoma	DMEM + 10%FBS
Intov-2	Adenocarcinoma	RPMI 1640+ 10% FCS+ LGlu+ 50uL β ME +1% Na Pyr
Jama-2	None given	RPMI 1640 +10% FBS + L-Glu
LK1	Teratocarcinoma from ascites	RPMI 1640 +10% FBS + L-Glu
LK2	None given	RPMI 1640 +10% FBS + L-Glu
MPSC1	Low-grade serous carcinoma	RPMI 1640 +10% FBS
OAW 42	Serous cystadenocarcinoma	DMEM + 10% FBS + Na Pyr + 20ug/ml Insulin + L-Glu
OC 316	Serous adenocarcinoma from ascites, with metastasis	RPMI 1640 +10% FBS
Ovca 433	Serous papillary cystadenocarcinoma	MEM EAGLE + 10% FBS
Ovcar-10	Adenocarcinoma	RPMI 1640 +10% FBS
Ovcar-3	Adenocarcinoma, from ascites	RPMI 1640 +10% FBS
Ovcar 5	Adenocarcinoma	RPMI 1640 +10% FBS + L-Glu
Ovcar 8	Adenocarcinoma	RPMI 1640 +10% FBS + L-Glu
Scov3 IP	Moderately well differentiated adenocarcinoma from ascites, from xenograft	RPMI 1640 +10% FBS

Supplementary table 5: Genes and their known or predicted function within a 330kb region at 19p13 containing the risk associated SNPs rs8170 and rs2363956.

Gene Name	Location	Description	TCGA expression data in EOCS[1]		
			≤0.5	≥0.5	Ratio loss:gain
USHBP1	19p13	Usher syndrome 1C binding protein 1	0.153	0.065	2.353
MYO9B	19p13.1	myosin IXB	0.005	0.394	0.013
NR2F6	19p13.1	nuclear receptor subfamily 2, group F, member 6	0.051	0.579	0.088
MRPL34	19p13.1	mitochondrial ribosomal protein L34	0.074	0.306	0.242
CPAMD8	19p13.11	C3 and PZP-like, alpha-2-macroglobulin domain containing 8	0.194	0.565	0.343
NY-SAR-48	19p13.11	sarcoma antigen NY-SAR-48	0.005	0.792	0.006
USE1	19p13.11	unconventional SNARE in the ER 1 homolog (S. cerevisiae)	0.042	0.449	0.09
OCEL1	19p13.11	occludin/ELL domain containing 1	0.477	0.097	4.917
MERIT40 (C19orf62)	19p13.11	chromosome 19 open reading frame 62	0.009	0.704	0.013
ANKLE1 (ANKRD41)	19p13.11	ankyrin repeat domain 41	0.134	0.102	1.31
ABHD8	19p13.11	abhydrolase domain containing 8	0.097	0.329	0.294
DDA1	19p13.11	DET1 and DDB1 associated 1	No data	No data	-
TMEM16H	19p13.11	transmembrane protein 16H	0.005	0.88	0.006
GTPBP3	19p13.11	GTP binding protein 3 (mitochondrial)	0.009	0.856	0.011

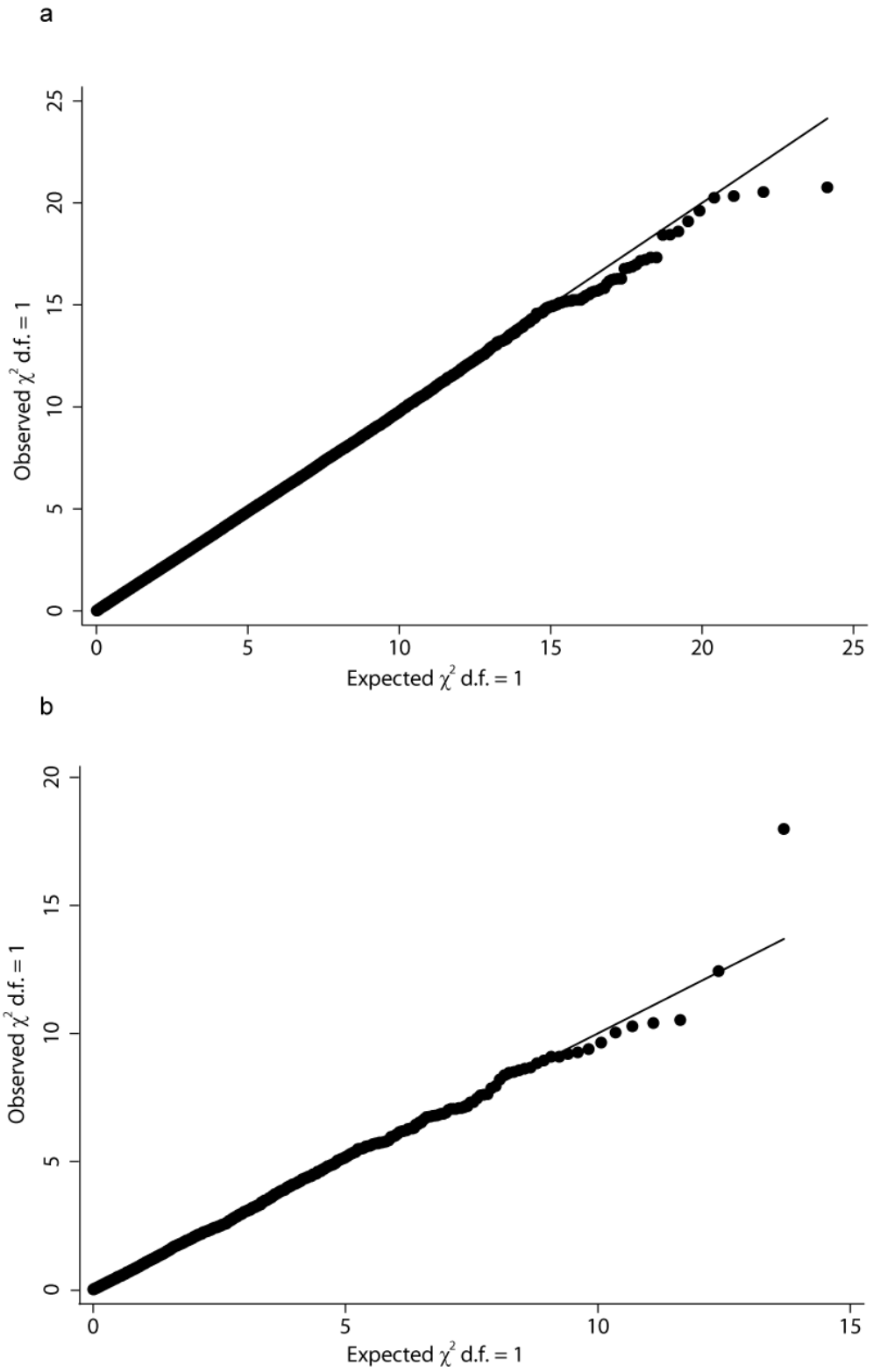
[1]Expression of candidate genes from ovarian cancer susceptibility locus in 216 serous ovarian tumors that are part of The Cancer Genome Atlas (TCGA). We have listed the proportion of tumors with >0.5 fold-change, up- and down-regulated expression, compared to the mean expression of these genes in pooled normal controls.

Supplementary table 6: Genotype quality control for Phase 3 studies for each SNP genotyped.

	Call Rate				Hardy Weinberg Equilibrium P-value		
	19p13		13q32		19p13		13q32
	rs2363956	rs8170	rs1125436		rs2363956	rs8170	rs1125436
BEL	100	100	98		0.85	0.30	0.22
GER	98	100	not genotyped		0.74	0.07	not genotyped
HAW	100	100	100		0.45	0.62	0.77
HJO+HMO	100	100	100		0.93	0.56	0.30
HOC	98	98	100		0.01	0.06	0.71
NTH	99	99	100		0.96	0.71	0.62
OVA	100	100	100		0.60	0.94	0.65
SOC+UKO	100	100	100		0.04	0.14	0.85
UCI	100	100	100		0.84	0.63	0.47
TCGA*	99	100	100		0.92	0.59	0.82
LAX*	97	100	100		0.001	0.32	0.38
PVD*	92	100	100		0.95	0.42	0.29
SCO*	100	100	100		0.84	0.67	0.40
HOP*	98	100	98		0.98	0.42	0.23
MAY	100	100	100		0.54	0.46	0.15
NCO	100	100	100		0.14	0.27	0.01
TBO	100	100	99		0.46	0.65	0.05
BWH	100	100	100		0.87	0.8	0.78
TOR	100	100	100		0.27	0.14	0.65

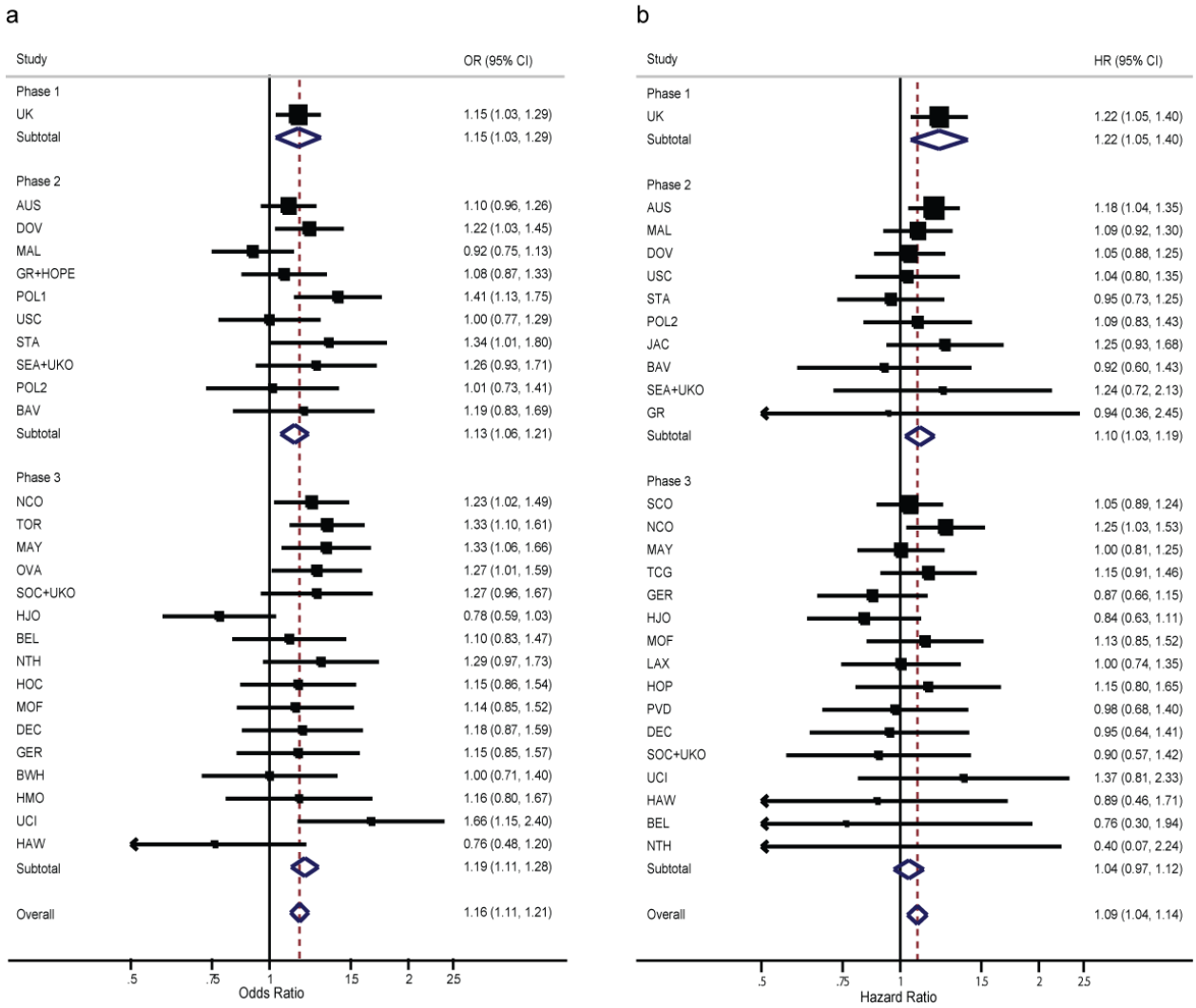
*These phase 3 studies were case-only and the Hardy Weinberg Equilibrium (HWE) P-value was calculated among cases. In the remaining studies, HWE was calculated among controls

Supplementary figure 1: Quantile-quantile plots for the test statistics of survival analyses.



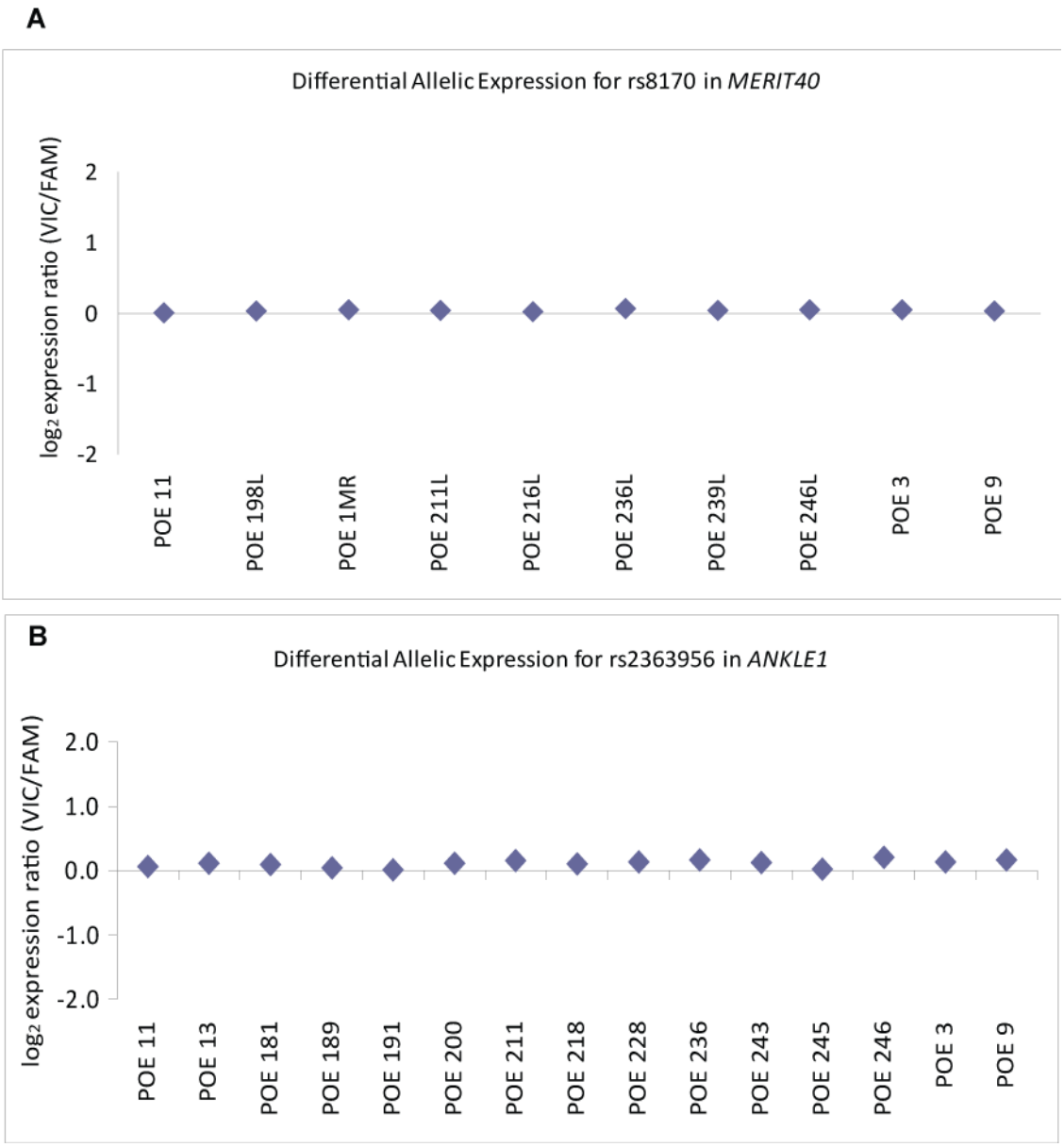
(a) Phase 1 survival analyses. (b) Phase 2 survival analyses.

Supplementary figure 2: Association of SNP rs2365936 with susceptibility to serous ovarian cancer and survival by phase and study**.**



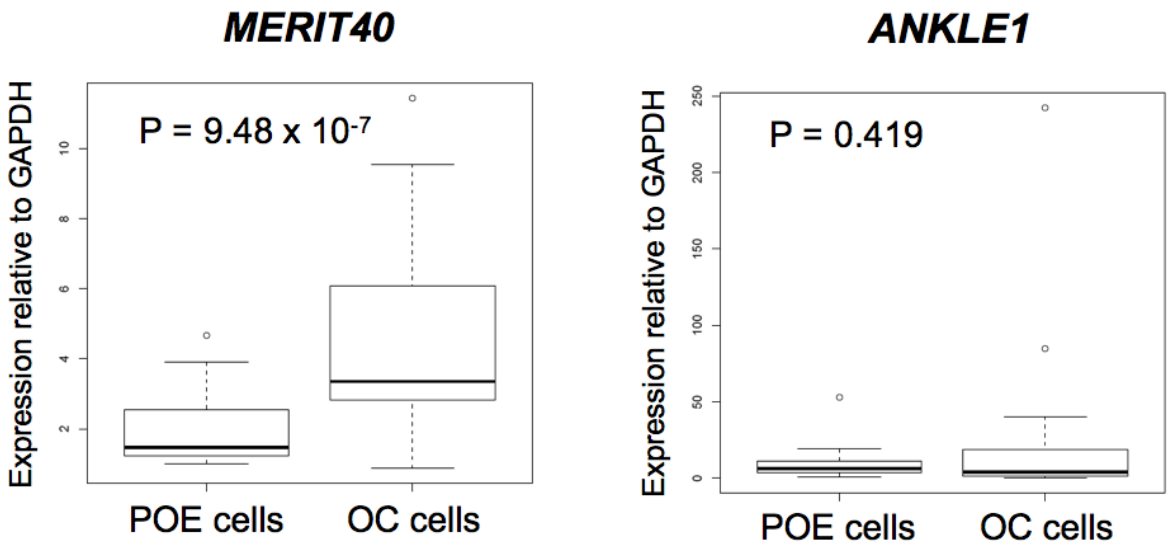
(a) Susceptibility to serous ovarian cancer. (b) Survival in all epithelial ovarian cancer cases.

Supplementary figure 3: Differential allelic expression analysis for rs8170 in *MERIT40* and rs2363956 in *ANKLE1* in primary ovarian epithelial (POE) cell lines.



Shown are the ratios of gene expression for (a) the C/T alleles of rs8170 in *MERIT40* for each heterozygous POE cell line and (b) the G/T alleles of rs2363956 in *ANKLE1* for each heterozygous POE cell line. The cut-off for differential allelic expression is $\log_2(1.20)=0.263$.

Supplementary figure 4: Gene expression analysis normalized to GAPDH for the *MERIT40* and *ANKLE1* genes, comparing expression in normal primary ovarian epithelial (POE) cell lines with ovarian cancer (OC) cell lines.



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