Published OnlineFirst November 22, 2013; DOI: 10.1158/0008-5472.CAN-13-1051

Prevention and Epidemiology

Cancer Research

Risk of Ovarian Cancer and the NF-κB Pathway: Genetic Association with *IL1A* and *TNFSF10*

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Abstract

A missense single-nucleotide polymorphism (SNP) in the immune modulatory gene *IL1A* has been associated with ovarian cancer risk (rs17561). Although the exact mechanism through which this SNP alters risk of ovarian cancer is not clearly understood, rs17561 has also been associated with risk of endometriosis, an epidemiologic risk factor for ovarian cancer. Interleukin-1α (IL1A) is both regulated by and able to activate NF-κB, a transcription factor family that induces transcription of many proinflammatory genes and may be an important mediator in carcinogenesis. We therefore tagged SNPs in more than 200 genes in the NF-κB pathway for a total of 2,282 SNPs (including rs17561) for genotype analysis of 15,604 cases of ovarian cancer in patients of European descent, including 6,179 of high-grade serous (HGS), 2,100 endometrioid, 1,591 mucinous, 1,034 clear cell, and 1,016 low-grade serous, including 23,235 control cases spanning 40 studies in the Ovarian Cancer Association Consortium. In this large population, we confirmed the association between rs17561 and clear cell ovarian cancer [OR, 0.84; 95% confidence interval (CI), 0.76–0.93; $P = 0.00075$], which remained intact even after excluding participants in the prior study (OR, 0.85; 95% CI, 0.75–0.95; $P = 0.006$). Considering a multiple-testing–corrected significance threshold of $P < 2.5 \times 10^{-5}$, only one other variant, the *TNFSF10* SNP rs6785617, was associated significantly with a risk of ovarian cancer (low malignant potential tumors OR, 0.85; 95% CI, 0.79–0.91; $P = 0.00002$). Our results extend the evidence that borderline tumors may have a distinct genetic etiology. Further investigation of how these SNPs might modify ovarian cancer associations with other inflammation-related risk factors is warranted. *Cancer Res; 74(3); 852–61. ©2013 AACR.*

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Introduction

Inflammation is a known mediator of carcinogenesis and several risk factors associated with ovarian cancer are also linked to inflammatory processes (1). The inverse relationship between parity (2, 3) and oral contraceptive use (3–6) and ovarian cancer risk is thought to be due to increased ovulations in women with fewer pregnancies or shorter duration of oral contraceptive use. The damage and repair cycle associated with each ovulation recruits immune mediators with potential to promote ovarian cancer initiation and growth (1, 7). Evidence for a relationship between pelvic inflammatory disease (PID) and ovarian cancer risk has also been observed in a few studies (8, 9). Furthermore, endometriosis, another condition associated with elevated inflammatory markers (10), has been found to increase risk of clear-cell, invasive endometrioid, and low-grade serous (LGS) tumors (11). Studies of perineal talcum powder use additionally suggest an association with ovarian cancer risk (12), presumably due to its proinflammatory properties (13). Use of nonsteroidal anti-inflammatory drugs (NSAID) has also been linked to reduced risk of ovarian cancer, particularly aspirin use in invasive ovarian cancer risk (14, 15).

In a previous study by our group, interrogation of single-nucleotide polymorphisms (SNP) in several inflammation-related genes revealed an association between ovarian cancer risk and SNPs in *IL1A* and *ALOX5* (16), most notable was a missense SNP in *IL1A*, rs17561, which had the strongest associations with the rarer histologic subtypes. Interleukin-1α (IL1A), the cytokine encoded by this gene, mediates a number of inflammatory and immune responses, including response to tissue injury (17, 18). In the present study, we assessed this SNP for overall and histologic subtype associations in a much larger population of ovarian cancer cases and controls to evaluate replication. We additionally investigated SNPs in other NF-κB pathway genes, as IL1A is not only

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Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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doi: 10.1158/0008-5472.CAN-13-1051

Published OnlineFirst November 22, 2013; DOI: 10.1158/0008-5472.CAN-13-1051

produced following NF-κB activation (19), but signaling of IL1A through its receptor also results in downstream activation of NF-κB (20), which leads to transcription of a number of genes whose products promote inflammation (21).

In addition to the prior association, there is strong biologic support for further study of polymorphisms in the NF-κB pathway in ovarian cancer (21). This pathway seems to play a crucial role in the process that links inflammation to cancer (22). Activation of this family of transcription factors leads to transcription and expression of a number of proinflammatory cytokines (23) with the ability to promote tumor growth (24). Specifically, activation of NF-κB through inhibitor of IκB kinase-ε (IKBKE) was shown to be associated with more aggressive behavior in ovarian cancer cell lines (25). In addition, NF-κB activation can inhibit apoptosis (26). Finally, NF-κB activation has been associated with aberrant cellular activities in endometriosis (27). Therefore, we expanded our investigation of inflammation-related SNPs to include variants in more than 200 NF-κB pathway–related genes in a large collection of patients with ovarian cancer and controls from the Ovarian Cancer Association Consortium (OCAC).

Patients and Methods

Study participants

Participants from 40 OCAC studies of primarily European ancestry were included in this project (28). For nine studies that were case-only (GRR, HSK, LAX, ORE, PVD, RMH, SOC, SRO, and UKR), cases were pooled with case–control studies from the same geographic region, resulting in 31 total case–control sets. Study characteristics are summarized in Supplementary Table S1 and the number of cases by histologic subtype is shown in Supplementary Table S2. A total of 47,092 women were included.

SNP selection

As reviewed previously (21), we identified a number of genes known to encode NF-κB subunits or molecules key to NF-κB activation (in signaling cascade), inhibition (inhibitory role), degradation (involved in proteasomal degradation), and nuclear function (nuclear proteins involved in transcription) and narrowed the list to the top 210 most important genes in the pathway. In early 2010, tagSNPs within 5 kb of these genes with $r^2 \geq 0.8$ and minor allele frequency (MAF) ≥ 0.05 in European individuals were identified using the most informative source for each gene from among HapMap Project Phase II Release 24 (29), the 1000 Genomes Project Low-coverage Pilot (30), SeattleSNPs (31), Innate Immunity PGA (32), and NIEHS SNPs (33). Additional putative-functional SNPs were also included, regardless of linkage disequilibrium, with European MAF $\geq$ 0.05 that were 1 kb upstream, nonsynonymous, or resided in a 3′-untranslated region (UTR), 5′-UTR, splice site, or miRNA-binding site (34, 35). We used SNPPicker (36) to optimally pick tagSNPs for each gene. SNPs that had an Illumina design score <0.4 or that were in linkage disequilibrium ($r^2 > 0.80$) with a SNP found to be null ($P > 0.05$) in prior analysis of genome-wide association study (GWAS) data (28) were excluded. Genes and coverage are shown in Supplementary Table S3.

Genotyping and quality control

Genotyping of study samples and duplicates, as previously described (28), was carried out as part of a large custom Illumina Infinium iSelect BeadChip (more than 200,000 SNPs) at McGill University and Génome Québec (Montreal, QC, Canada; $n = 19{,}806$) and the Mayo Clinic Medical Genome Facility (Rochester, MN; $n = 28{,}820$) on 96-well plates containing 750 ng genomic DNA (or 1,500 ng whole-genome amplified DNA). Along with OCAC samples, HapMap samples for European (CEU, $n = 60$), African (YRI, $n = 53$), and Asian (JPT+CHB, $n = 88$) populations were also genotyped. Raw intensity data files were reviewed for centralized quality control, and genotypes were called using GenCall (37), which showed superior performance over Illuminus (38) and GenoSNP (39) upon manual inspection of representative SNPs.

SNPs were excluded according to the following criteria: (i) no genotype call; (ii) monomorphism; (iii) call rate less than 95% and MAF > 0.05 or call rate less than 99% with MAF < 0.05; (iv) evidence of deviation from Hardy–Weinberg equilibrium ($P < 10^{-7}$) in controls; and (v) greater than 2% discordance in duplicate pairs. Overall, 94.5% of SNPs passed quality control; a total of 2,282 NF-κB SNPs were included in analyses.

SNP data were generated on 47,092 unique samples. We used identity-by-state to identify first-degree relative pairs, of which we excluded the one with the lowest call rate. Additional samples were excluded according to the following criteria: (i) call rates < 95%; (ii) heterozygosity > five standard deviations from the intercontinental ancestry-specific mean heterozygosity; (iii) ambiguous sex; (iv) lowest call rate from a first-degree relative pair; (v) missing case–control status; (vi) missing age at diagnosis; (vii) nonepithelial cancer, unknown if epithelial cancer or missing histology; (viii) Brenner tumors; and (ix) <90 European ancestry based on local ancestry in admixed populations (LAMP; ref. 40). After the above exclusions, a total of 38,839 subjects including 15,604 cases (13,727 invasive) and 23,235 controls were retained for analysis (Supplementary Table S4).

Statistical methods

SNP genotypes were coded as 0, 1, or 2 based on the number of copies of the minor allele. Associations with risk of ovarian cancer were evaluated first using cases combined, and then within strata defined by tumor behavior [low malignant potential (LMP) and invasive] and histology [LGS, high-grade serous (HGS), mucinous, endometrioid, and clear cell]. We used a subset of 37,000 non-NF-κB markers to perform principal component (PC) analysis within the European subset to account for potential residual population stratification (41). For all analyses, SNPs were modeled using a one degree-of-freedom linear term assuming a log-additive, or ordinal, effect. OR, 95% confidence intervals (CI), and P values were generated using logistic regression analysis in PLINK (Version 1.07; ref. 42) with adjustment for age, study site, and the first five European PCs as described above. Effect modification by site and epidemiologic risk factors were tested using interaction terms and differences in risk by subtype were tested using multicategorical (polytomous) regression.

SNPs reported in Tables 1–3 were additionally tested for confounding by the following epidemiologic risk factors in the

Published OnlineFirst November 22, 2013; DOI: 10.1158/0008-5472.CAN-13-1051

subset of study sites with information on each epidemiologic variable: acetaminophen use [nonregular (<1×/week), regular (≥1×/week)], aspirin use [nonregular (<1×/week), regular (≥1×/week)], non-aspirin NSAID use [nonregular (<1×/week), regular (≥1×/week)], young adult body mass index [BMI; continuous (age 18 or 20 years)], recent BMI [continuous (1 or 5 years before diagnosis)], history of endometriosis (yes, no), history of breast or ovarian cancer in a first-degree relative (none, ≥1 relative), age at menarche (≤11, >11 years), menopausal status at diagnosis (pre/peri, post), ever use of oral contraceptives (yes, no), and ever use of estrogen after age of 50 years (yes, no). None of these variables changed the estimates by more than 10% for any of the SNPs with sufficient numbers in the subsets to calculate stable estimates.

Pairwise linkage disequilibrium among controls was estimated using PLINK (42). Results [$-\log_{10}$ (P value)] for regions of interest were visualized using LocusZoom (Standalone Version; ref. 43), which included user-specified linkage disequilibrium as defined above. The SNP examined in a previous study, *IL1A* rs17561, was reevaluated in this study for replication purposes using a nominal P value of 0.05. We used a modified Bonferroni-adjusted critical value to determine statistical significance of all other newly studied NF-κB SNPs. To account for linkage disequilibrium between SNPs, a qr decomposition of the SNP genotype matrix (44) was used to determine the effective number of independent tests. Genotypes for 2,282 NF-κB pathway SNPs with a MAF > 0.01 from a random sample of 1,000 epithelial ovarian cancer cases and 1,000 controls were considered. The number of independent tests (i.e., the rank of the SNP genotype matrix) was determined to be 2,000, thus yielding a Bonferroni-adjusted critical value of 2.5×10^{-5} (0.05/number of independent tests).

Results

Replication of *IL1A* SNP rs17561 in ovarian cancer risk

The missense SNP, rs17561, in the *IL1A* gene, previously reported by our group to be significantly associated with clear cell, mucinous, and endometrioid ovarian cancer risk in a subset of OCAC studies (3,972 cases and 3,043 controls; ref. 16), was reevaluated using a larger number of participants (15,604 cases and 23,235 controls). This included 6,179 HGS, 2,100 endometrioid, 1,591 mucinous, 1,034 clear cell, and 1,016 LGS ovarian cancer cases. In this larger pooled study, we found no association between rs17561 and risk of all ovarian cancer; however, when we stratified by histologic subtype, we found modest inverse associations with the minor allele of this SNP and risk of endometrioid (OR, 0.93; 95% CI, 0.87–1.00; $P = 0.053$) and mucinous subsets (OR, 0.91; 95% CI, 0.84–0.98; $P = 0.018$) and a stronger inverse association with the minor allele of this SNP and clear cell ovarian cancer (OR, 0.84; 95% CI, 0.76–0.93; $P = 0.00075$; Fig. 1). As the previous report of rs17561 describing an association with clear cell ($N = 283$ cases) ovarian cancer included a subset of the current study population (16), we restricted our analysis to exclude all participants from the prior study and found that the inverse association between the minor allele of this SNP and risk of clear cell ($N = 734$ cases) disease remained (OR, 0.85; 95% CI, 0.75–0.95; $P = 0.006$).

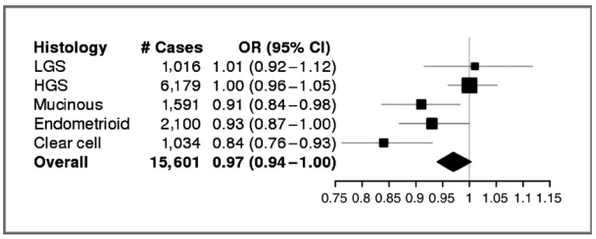

Figure 1. *IL1A* SNP, rs17561, associations with risk of ovarian cancer by subtype. Forest plots of OR and 95% CI for HGS, LGS, mucinous, endometrioid, clear cell, and overall ovarian cancer.

The major allele of rs17561 has also recently been reported to be associated with increased risk of endometriosis in a pooled Japanese case–control study (45). History of endometriosis was obtained for several studies in OCAC via self-report. Given the link between endometriosis and clear cell ovarian cancer (11), we chose to assess the association between endometriosis and rs17561 in the European ancestry OCAC population, where we observed the association between this SNP and clear cell ovarian cancer. Although we found a trend in the direction of decreased risk of endometriosis with the minor allele of rs17561 (OR, 0.93; 95% CI, 0.82–1.05) among the 10,759 controls with available genotype and endometriosis information, it was not statistically significant ($P = 0.25$).

We additionally evaluated whether any of the epidemiologic risk factors for ovarian cancer listed in Supplementary Table S5 modified the association between rs17561 and risk of clear cell ovarian cancer. There was little evidence for interaction between rs17561 and any of these factors, with the exception of a modest interaction with NSAID use ($P = 0.046$). When stratified by NSAID use, the inverse association between rs17561 and clear cell ovarian cancer risk was observed among regular NSAID users (OR, 0.71; 95% CI, 0.54–0.95), but null among nonregular NSAID users (OR, 1.01; 95% CI, 0.84–1.20).

Overall ovarian cancer risk associations with NF-κB pathway SNPs

A total of 2,281 additional SNPs in 210 genes in the NF-κB were also analyzed. When ranked by P value, the most significant SNPs in the NF-κB pathway found to be associated with overall (includes LMP) ovarian cancer risk at $P < 0.005$ were located in *CARD11*, *FBXW7*, *IL1RAPL2*, *IRAK2*, *MAP3K14*, *NFKB1*, *PRKCA*, *TAF3*, *TLR7*, *TNFRSF1B*, and *TNFSF10* genes (Table 1); however, none of these SNPs reached statistical significance after multiple testing correction. A *CARD11* SNP rs74302019 had the lowest P value (OR, 1.07; 95% CI, 1.03–1.10; $P = 8.91 \times 10^{-05}$), and four of 57 SNPs tagged in *CARD11* were associated with ovarian cancer risk at $P < 0.005$, although rs41324349 and rs41483047 were in moderate linkage disequilibrium with rs74302019 with $r^2 = 0.61$ and 0.41, respectively.

Tumor behavior associations with NF-κB pathway SNPs

We also assessed NF-κB pathway SNPs according to tumor behavior (invasive or LMP). All SNPs associated with tumor

Published OnlineFirst November 22, 2013; DOI: 10.1158/0008-5472.CAN-13-1051

Table 1. Top NF-κB pathway SNPs ($P < 0.005$) associated with overall ovarian cancer[a] risk

Gene	SNP[b]	Chrm	Location	Minor	Major	MAF (case)	MAF (control)	OR[c] (95% CI)	P[c]
TNFRSF1B	rs17884213	1	Intron	A	G	26.7	26	1.05 (1.02–1.09)	0.002
TNFSF10	rs6801105	3	Intron	A	G	16.7	17.4	0.94 (0.90–0.98)	0.002
IRAK2	rs459483	3	Intron	G	A	45.2	46.3	0.95 (0.93–0.98)	0.003
TNFSF10	rs1131535	3	3′-UTR	A	G	43.2	44.3	0.96 (0.93–0.99)	0.004
FBXW7	rs75911772	4	Intron	T	A	3.9	3.5	1.14 (1.05–1.23)	0.002
NFKB1	rs1609993	4	Synonymous	A	G	8.8	8	1.08 (1.03–1.14)	0.003
CARD11	**rs74302019**	7	Intron	A	G	32.2	31.1	1.07 (1.03–1.10)	**8.9×10^{-05}**
CARD11	**rs41324349**	7	Intron	A	C	43	41.6	1.06 (1.03–1.09)	**0.0002**
CARD11	**rs41483047**	7	Intron	A	G	18.5	17.6	1.07 (1.03–1.12)	**0.0004**
CARD11	rs35329971	7	Intron	A	G	8.8	9.6	0.92 (0.87–0.97)	0.002
TAF3	**rs7071113**	10	3′ Downstream	C	G	31.8	30.8	1.06 (1.03–1.10)	**0.0003**
TAF3	rs1244229	10	Val696Ala	A	G	30	29.1	1.06 (1.02–1.09)	0.001
TAF3	rs263417	10	Intron	A	C	30.2	29.4	1.05 (1.02–1.09)	0.002
TAF3	rs1514233	10	Intron	T	A	30.3	29.5	1.05 (1.02–1.09)	0.003
PRKCA	rs7226221	17	Intron	G	A	39.1	40.2	0.95 (0.92–0.98)	0.002
MAP3K14	rs9908462	17	Intron	A	G	19	19.8	0.94 (0.91–0.98)	0.003
IL1RAPL2	rs1384360	23	Intron	A	C	26.6	25.7	1.06 (1.02–1.09)	0.001
TLR7	rs5743733	23	Intron	G	C	8.8	8.1	1.09 (1.03–1.15)	0.003

[a]Includes invasive and borderline tumor behavior.
[b]SNPs are listed first by chromosome and then ranked by ordinal *P* value within the chromosome.
[c]Ordinal OR and *P* value, adjusted for first five PCs, age, and study site. Bold values highlight $P < 0.001$.

behavior at $P < 0.005$ are reported in Table 2. SNPs in *IL1RAPL2*, *OTUD7B*, *PLCG1*, *TAF4*, *TLR5*, *TNFSF10*, and *TRAF2* were suggestively associated with LMP ovarian tumors at $P < 0.005$. One SNP in *TNFSF10* was statistically significantly associated with LMP risk after adjustment for multiple testing, rs6785617 (OR, 0.85; 95% CI, 0.79–0.91; $P = 2.0 \times 10^{-5}$). We further evaluated this association for effect modification by epidemiologic risk factors previously reported in association with ovarian cancer, but we found little evidence for interaction (Supplementary Table S5).

No NF-κB pathway SNPs were associated with risk of invasive ovarian cancer at $P < 2.5 \times 10^{-5}$. However, the SNP associated with risk of invasive ovarian cancer with the lowest *P* value was rs7071113 (OR, 1.06; 95% CI, 1.02–1.10; $P = 0.00087$) in *TAF3* and suggestive associations were observed at $P < 0.005$ for other SNPs in *TAF3* as well as *CARD11*, *FBXW7*, *IL1RN*, *IRAK2*, *MAP3K7*, *TAB2*, *PRKDC*, and *TNFRSF1B*.

Histologic subtype associations with NF-κB pathway SNPs

Although no SNPs were associated with risk at the corrected level of 2.5×10^{-5} for any histologic subtypes (Table 3), the missense SNP rs17561 (reported above) in the *IL1A* gene, was the NF-κB pathway SNP that had the lowest *P* value in association with clear cell ovarian cancer risk (OR, 0.84; 95% CI, 0.76–0.93; $P = 0.00075$); four other *IL1A* SNPs, rs1800587, rs1304037, rs2856836, and rs1800794 were also inversely associated with ovarian cancer risk at $P < 0.005$ as expected on the basis of near complete linkage disequilibrium with rs17561 ($r^2 > 0.99$). Other SNPs that were suggestively associated with clear cell ovarian cancer at $P < 0.005$ were found in *AKT1*, *BCL10*, *CD3E*, *IKBKE*, *IL1RN*, *NFKBIZ*, *PPARG*, *TLR3*, and *TLR7*. For endometrioid ovarian cancer *MTOR* SNP, rs12129467, had the lowest *P* value with a suggestive association (OR, 1.19; 95% CI, 1.07–1.33; $P = 0.0013$); this SNP was the only tagSNP in this gene of 10 genotyped with $P < 0.005$ (data not shown). Other SNPs with potential associations for endometrioid ovarian cancer risk at $P < 0.005$ were found in the *F2R*, *IKBKAP*, and *HNRNPAB* genes. Mucinous ovarian cancer was potentially ($P < 0.005$) associated with SNPs in *CD247*, *IL1A*, *PRKCA*, *PRKCQ*, *PRKCZ*, *PTPN13*, *TLR1*, *TLR10*, and *TNFSF10*. The SNP with the lowest *P* value was rs34251715, an intronic SNP in *PRKCA* (OR, 0.88; 95% CI, 0.82–0.96; $P = 0.0028$).

The SNPs suggestively associated with risk of HGS ovarian cancer at $P < 0.005$ were located in *AARB2*, *CARD11*, *IL1RN*, *MAP3K14*, *PIK3R1*, *PRKCA*, *PRKCZ*, *PRKDC*, *TLR5*, and *TNFRSF1B*. *CARD11* SNP, rs71527417, had the lowest *P* value for HGS ovarian cancer risk (OR, 0.87; 95% CI, 0.80–0.95; $P = 0.0015$), although the association was not significant at the multiple comparisons threshold. Two other SNPs in this gene, rs74302019 and rs41324349, were also associated with HGS, at $P < 0.005$ and the association was in the opposite direction (linkage disequilibrium with rs71527417: $r^2 = 0.03$ and 0.05, respectively). For LGS ovarian cancer risk, the association with the lowest *P* value was with intronic SNP, rs3136646, located in *NFKBIB* (OR, 0.81; 95% CI, 0.72–0.91; $P = 0.00034$). Additional possible associations with LGS at $P < 0.005$ included SNPs from *GSK3B*, *IKBKAP*, and *PRKCA*.

Published OnlineFirst November 22, 2013; DOI: 10.1158/0008-5472.CAN-13-1051

Table 2. Top NF-κB pathway SNPs ($P < 0.005$) associated with invasive and LMP tumor behavior

Case group	Gene	SNP[a]	Chrm	Location	Minor	Major	MAF (case)	MAF (control)	OR[b] (95% CI)	P^b
Invasive ($N = 13,727$)	*TNFRSF1B*	**rs17884213**	1	Intron	A	G	26.8	26	**1.06 (1.02–1.10)**	**0.00097**
	IL1RN	rs62161280	2	3′ Downstream	G	A	5.7	5.2	1.11 (1.03–1.18)	0.004
	IRAK2	rs459483	3	Intron	G	A	45.2	46.3	0.95 (0.92–0.98)	0.003
	FBXW7	rs75911772	4	Intron	T	A	3.9	3.5	1.13 (1.05–1.23)	0.003
	MAP3K7	rs80138790	6	3′ Downstream	A	G	3.7	3.3	1.14 (1.05–1.24)	0.002
	TAB2	rs573148	6	5′ Upstream	G	A	37	38.1	0.96 (0.92–0.99)	0.005
	CARD11	**rs41324349**	7	Intron	A	C	42.9	41.6	**1.05 (1.02–1.09)**	**0.0009**
	CARD11	**rs74302019**	7	Intron	A	G	32.1	31.1	**1.06 (1.02–1.10)**	**0.0009**
	CARD11	rs41483047	7	Intron	A	G	18.4	17.6	1.07 (1.03–1.11)	0.001
	PRKDC	rs74915527	8	Intron	A	G	10.5	9.8	1.08 (1.03–1.14)	0.003
	TAF3	**rs7071113**	10	3′ Downstream	C	G	31.8	30.8	**1.06 (1.02–1.10)**	**0.0009**
	TAF3	rs1244229	10	Val696Ala	A	G	29.9	29.1	1.05 (1.02–1.09)	0.004
LMP ($N = 1,729$)	*OTUD7B*	rs41265172	1	3′-UTR	A	G	4.8	3.9	1.3 (1.09–1.55)	0.004
	TLR5	rs2241097	1	Intron	C	A	27.1	25.4	1.13 (1.04–1.23)	0.004
	TNFSF10	**rs6785617**	3	3′ Downstream	T	A	43.1	46.2	0.85 (0.79–0.91)	**2.0×10^{-05}**
	TNFSF10	**rs6801105**	3	Intron	A	G	15.6	17.4	0.84 (0.76–0.93)	**0.0008**
	TRAF2	**rs17243893**	9	Intron	G	A	4.8	5.7	0.75 (0.63–0.88)	**0.0007**
	PLCG1	rs12625708	20	Intron	A	C	18.7	21	0.86 (0.78–0.94)	0.001
	TAF4	rs744779	20	Intron	A	G	23.8	22	1.14 (1.05–1.25)	0.003
	IL1RAPL2	**rs1384360**	23	Intron	A	C	28.6	25.7	1.15 (1.06–1.25)	**0.0009**

[a]SNPs are listed first by chromosome and then ranked by ordinal *P* value within the chromosome.
[b]Ordinal OR and *P* value, adjusted for first five PCs, age, and study site. Bold values highlight $P < 0.001$.

Discussion

In this large study of 15,604 ovarian cancer cases and 23,235 controls of European descent, we assessed the rs17561 SNP, previously found by our group to be associated with overall ovarian cancer risk. When analyzed by histologic subtypes, there were modest associations with risk of mucinous and endometrioid subtypes and a fairly strong association with risk of clear cell, all of which are consistent with our previous study (16). The clear cell association remained even after exclusion of participants in the prior report. In this same large study population, assessment of additional variants in more than 200 genes in the NF-κB pathway pointed to some suggestive associations with ovarian cancer risk. The most significant SNPs associated with each subtype tended to be located in different genes. However, with the exception of rs6785617 and LMP tumors, none of these SNPs reached our critical *P* value of 2.5×10^{-5}.

The missense SNP in *IL1A*, rs17561, results in an amino acid change at position 114 from alanine (major allele) to serine (minor allele). Enhanced cleavage of the IL1A precursor (46) has been reported to be the functional consequence of a serine residue at this position and calpain cleaved IL1A seems to bind IL-1 receptor 1 (IL1R1) with higher affinity, resulting in higher cytokine expression than the uncleaved form (47). The major allele (A) of rs17561 has recently been reported to be associated with increased susceptibility to endometriosis in two independent case–control studies in a Japanese population (45). This is consistent with our finding in the present study that the minor allele is associated with decreased risk of clear cell ovarian cancer, and is especially interesting given the previous associations found between endometriosis and clear cell ovarian cancer (11), suggesting a potential shared biologic mechanism. When we evaluated this SNP for association with endometriosis in the European ancestry OCAC population, we saw little evidence for an association between rs17561 and endometriosis. The lack of association in the OCAC population could potentially be attributed to other genetic differences between Japanese and European ancestry populations. However, we also note that in the present study we are limited by questionnaire-based self-reported history of endometriosis, whereas the Japanese study used clinical imaging or biopsy confirmation to ascertain diagnosis of endometriosis.

Recently, Trabert and colleagues reported a statistically significant association between regular aspirin use and a modest nonsignificant association with non-aspirin NSAID use and decreased risk of invasive ovarian cancer in the OCAC population (15). Interestingly, we find that the association between rs17561 and clear cell risk seems to be modified by non-aspirin NSAID use, where the inverse association with the minor allele is found among regular NSAID users but is null in nonregular NSAID users. The role of IL1A on tumor development is complex, depending on whether it has been processed, whether it is membrane-bound or secreted, and which stage in tumorigenesis and cell type it is expressed, it may play a role in immune surveillance or tumor progression (48). One potential mechanism through which NSAIDs may influence the effects of IL1A on tumor growth is through inhibition of prostaglandin synthesis by COX-2 (49), which is expressed following IL1A signalling through IL1R1. NSAID use has also been reported to

Published OnlineFirst November 22, 2013; DOI: 10.1158/0008-5472.CAN-13-1051

Table 3. Top NF-κB pathway SNPs ($P < 0.005$) associated with risk of ovarian cancer histologic subtypes[a]

Case group	Gene	SNP[b]	Chrm	Location	Minor	Major	MAF (case)	MAF (control)	OR[c] (95% CI)	P[c]
HGS ($N = 6,179$)	*TLR5*	rs116693072	1	5′ Upstream	G	A	4.5	4	1.18 (1.06–1.30)	0.002
	TNFRSF1B	rs17884213	1	Intron	A	G	26.9	26	1.07 (1.02–1.13)	0.004
	PRKCZ	rs9729600	1	Intron	A	G	9.5	9.3	1.11 (1.03–1.19)	0.005
	IL1RN	rs62161280	2	3′ Downstream	G	A	5.8	5.2	1.14 (1.04–1.25)	0.004
	PIK3R1	rs72757693	5	Intron	A	G	13.9	13.2	1.1 (1.03–1.17)	0.003
	PIK3R1	rs12755	5	3′-UTR	A	C	17.8	16.8	1.09 (1.03–1.15)	0.004
	CARD11	rs71527417	7	Intron	A	C	6.3	7.2	0.87 (0.80–0.95)	0.002
	CARD11	rs74302019	7	Intron	A	G	32.3	31.1	1.07 (1.03–1.12)	0.003
	CARD11	rs41324349	7	Intron	A	C	43.1	41.6	1.06 (1.02–1.11)	0.005
	PRKDC	rs74915527	8	Intron	A	G	10.6	9.8	1.11 (1.04–1.19)	0.004
	MAP3K14	rs117642368	17	5′ Upstream	G	C	11.6	10.5	1.1 (1.03–1.18)	0.004
	ARRB2	rs28365157	17	Intron	A	G	9.6	10	0.9 (0.84–0.97)	0.005
	PRKCA	rs28733563	17	Intron	A	G	24.7	23.4	1.07 (1.02–1.13)	0.005
Endometrioid ($N = 2,100$)	*MTOR*	rs12129467	1	Intron	C	G	10.2	8.7	1.19 (1.07–1.33)	0.001
	F2R	rs253073	5	Intron	G	A	46.2	43.7	1.11 (1.04–1.18)	0.002
	HNRNPAB	rs116592017	5	5′ Upstream	A	C	2.1	2.9	0.72 (0.58–0.89)	0.003
	IKBKAP	rs2230792	9	Gly765Ala	A	G	20.3	18.6	1.13 (1.04–1.22)	0.004
Mucinous ($N = 1,591$)	*PRKCZ*	rs34415348	1	Intron	C	A	9.2	10.8	0.83 (0.73–0.94)	0.004
	CD247	rs1773539	1	Intron	A	G	4.9	3.9	1.29 (1.08–1.53)	0.004
	IL1A	rs150712565	2	Intron	A	T	32.5	29.9	1.12 (1.04–1.22)	0.004
	TNFSF10	rs12488654	3	5′ Upstream	A	G	18.9	16.7	1.15 (1.05–1.26)	0.004
	PTPN13	rs62308410	4	Intron	A	G	46.5	43.9	1.12 (1.04–1.20)	0.004
	TLR1	rs5743551	4	5′ Upstream	G	A	20.9	23.9	0.88 (0.80–0.96)	0.004
	TLR10	rs4274855	4	5′-UTR	A	G	15.3	17.7	0.86 (0.78–0.96)	0.005
	PRKCQ	rs4750528	10	Intron	G	A	15.5	17.6	0.86 (0.78–0.95)	0.004
	PRKCA	rs34251715	17	Intron	G	A	28.9	31.8	0.88 (0.82–0.96)	0.003
Clear cell ($N = 1,034$)	*IKBKE*	rs41296022	1	Intron	A	G	4.7	3.4	1.37 (1.11–1.70)	0.004
	BCL10	rs2735593	1	5′-UTR	C	G	24.1	21.5	1.16 (1.05–1.29)	0.005
	IL1A	**rs17561**	2	Ala114Ser	A	C	26.8	30.2	**0.84 (0.76–0.93)**	**0.0008**
	IL1A	**rs1800587**	2	5′-UTR	A	G	26.8	30.2	**0.84 (0.76–0.93)**	**0.0008**
	IL1A	**rs1304037**	2	3′-UTR	G	A	26.8	30.1	**0.84 (0.76–0.93)**	**0.0008**
	IL1A	**rs2856836**	2	3′-UTR	G	A	26.8	30.2	**0.85 (0.76–0.93)**	**0.00099**
	IL1A	rs1800794	2	5′ Upstream	A	G	26.7	30	0.85 (0.77–0.94)	0.001
	IL1RN	rs2071459	2	Intron	A	G	10.6	13	0.81 (0.70–0.94)	0.004
	NFKBIZ	rs80099440	3	Intron	A	G	6.5	4.9	1.36 (1.13–1.63)	0.001
	PPARG	rs77323418	3	3′ Downstream	G	A	3.4	4.7	0.7 (0.55–0.89)	0.004
	TLR3	rs66624661	4	Intron	A	G	36.5	33.7	1.14 (1.04–1.25)	0.005
	CD3E	rs73014299	11	3′ Downstream	A	G	8.8	11.1	0.78 (0.67–0.91)	0.002
	AKT1	rs45531934	14	Intron	A	G	5.6	7.2	0.74 (0.60–0.90)	0.003
	TLR7	rs5743733	23	Intron	G	C	10.1	8.1	1.26 (1.09–1.46)	0.002
LGS ($N = 1,016$)	*GSK3B*	rs13320980	3	Intron	G	A	28.7	31.9	0.86 (0.78–0.96)	0.005
	IKBKAP	rs10117384	9	Intron	A	G	18.5	21.7	0.84 (0.74–0.94)	0.003
	PRKCA	rs7226221	17	Intron	G	A	36.9	40.2	0.87 (0.79–0.96)	0.004
	NFKBIB	**rs3136646**	19	Intron	A	G	20.3	23.8	**0.81 (0.72–0.91)**	**0.0003**

[a]Subtype analyses included invasive and LMP cases.

[b]SNPs are listed first by chromosome and then ranked by ordinal *P* value within the chromosome.

[c]Ordinal OR and *P* value, adjusted for first five PCs, age, and study site. Bold values highlight $P < 0.001$.

interact with *IL1* SNP haplotypes in risk of B-cell non-Hodgkin lymphoma (50).

TNFSF10, also known as TRAIL, induces a signaling cascade that leads to apoptosis upon binding either of its cognate death receptors, DR4 (TNFRSF10A) and DR5 (TNFRSF10B; ref. 51). This ligand has been of particular interest for use in cancer therapy, as many cancer cell types are more sensitive to TNFSF10-induced cell death than normal cells (52). TRAIL is also important in immune surveillance of tumor cells (53) and plays a role in controlling inflammation by inducing apoptosis in macrophages (54) and neutrophils (55). The only novel NF-κB SNP to pass our significance threshold was *TNFSF10* SNP, rs6785617, in association with LMP tumor behavior. This SNP falls 4.5 kb downstream of this gene, and to our knowledge it has not previously been reported to be associated with ovarian tumors or other conditions, nor have

Published OnlineFirst November 22, 2013; DOI: 10.1158/0008-5472.CAN-13-1051

consequences of this SNP on expression or function been tested experimentally.

CARD11 is an intermediate protein that assists in NF-κB activation following B- or T-cell receptor complex ligation (56–58) or activation of natural killer (NK) cell receptors (59). *CARD11* intronic SNPs, rs74302019, rs41324349, and rs41483047 are in moderate linkage disequilibrium with each other and had the lowest *P* values associated with overall ovarian cancer risk. To our knowledge, none of the have been previously assessed for associations with ovarian cancer or other conditions and their consequences on CARD11 function or expression are unclear. Although aberrant expression in tumors is possible, CARD11, also known as CARMA1, is normally expressed in cells of hematopoietic origin (60), suggesting that the role of this polymorphism in ovarian cancer risk may be related to tumor surveillance by immune cells.

This study has several strengths, the most notable of which is the very large sample size that provided greater power than all previous candidate gene studies in ovarian cancer to detect associations between this disease and SNPs with lower MAF. We also had greater power to assess associations between the less common subtypes: endometrioid, clear cell, and mucinous ovarian cancer. We used a SNP tagging approach to comprehensively cover genes in the NF-κB pathway; however, the study was limited by lack of coverage of some genes, mostly due to loss of SNPs that failed quality control. Nonetheless, this is the first study to extensively assess variation in genes involved in NF-κB activition, including signaling, inhibition, degradation, and nuclear function in association with ovarian cancer risk. Because of variation in MAF by race, we restricted our analysis to participants of genetic European descent, which reduces confounding but also generalizability to other populations. Because only one SNP was associated with risk of LMP tumors below the multiple test–corrected *P* value, we cannot rule out that any of the suggestive associations were actually false positives.

In conclusion, this large study of NF-κB pathway genes in relation to risk of ovarian cancer found several SNPs with suggestive associations that varied by histology and tumor behavior. All SNP associations were modest, but most interesting were the replication of *IL1A* SNP, rs17561, in clear cell risk and the association between *TNFSF10* SNP, rs6785617, and LMP ovarian cancer. Future investigations of interactions between these polymorphisms and environmental factors, the role they play on tumor phenotypes, and how they affect NF-κB activity in different cell types are needed to better understand the mechanism by which they might be contributing to ovarian cancer pathogenesis.

Disclosure of Potential Conflicts of Interest

U. Menon has an expert testimony from Abcodia Ltd. B. Charbonneau was an employee of Mayo Clinic at the time this manuscript was drafted and is currently an employee of and owns stock in Eli Lilly and Company. No potential conflicts of interest were disclosed by the other authors.

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Acknowledgments

The authors thank all the individuals who took part in this study and all the researchers, clinicians, and administrative staff who have made possible the many studies contributing to this work. In particular, the authors thank: D. Bowtell, A. deFazio, D. Gertig, A. Green, P. Parsons, N. Hayward, and D. Whiteman (AUS); G. Peuteman, T. Van Brussel, and D. Smeets (BEL); U. Eilber and T. Koehler (GER); L. Gacucova (HMO); P. Schurmann, F. Kramer, W. Zheng, T.-W. Park-Simon, K. Beer-Grondke, and D. Schmidt (HJO); Sharon Windebank, Christopher Hilker, and Jason Vollenweider (MAY); the state cancer registries of AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, and WYL (NHS); L. Paddock, M. King, L. Rodriguez-Rodriguez, A. Samoila, and Y. Bensman (NJO); M. Sherman, A. Hutchinson, N. Szeszenia-Dabrowska, B. Peplonska, W. Zatonski, A. Soni, and M. Stagner (POL); C. Luccarini, P. Harrington the SEARCH team, and ECRIC (SEA); the Scottish Gynaecological Clinical Trails group and SCOTROC1 investigators (SRO); I. Jacobs, M. Widschwendter, E. Wozniak, N. Balogun, A. Ryan, and J. Ford (UKO); Carole Pye (UKR). This study would not have been possible without the contributions of the following: Per Hall (COGS); Douglas F. Easton (BCAC); Andrew Berchuck (OCAC); Rosalind A. Eeles, Douglas F. Easton, Ali Amin Al Olama, Zsofia Kote-Jarai (PRACTICAL); Georgia Chenevix-Trench, Antonis Antoniou, Fergus Couch, and Ken Offit (CIMBA); Joe Dennis, Alison M. Dunning, Andrew Lee, and Ed Dicks (Cambridge); Javier Benitez, Anna Gonzalez-Neira, and the staff of the CNIO genotyping unit, Jacques Simard and Daniel C. Tessier, Francois Bacot, Daniel Vincent, Sylvie LaBoissière, and Frederic Robidoux and the staff of the McGill University and Génome Québec Innovation Centre, Stig E. Bojesen, Sune F. Nielsen, Borge G. Nordestgaard, and the staff of the Copenhagen DNA laboratory, and Julie M. Cunningham, Sharon A. Windebank, Christopher A. Hilker, Jeffrey Meyer and the staff of Mayo Clinic Genotyping Core Facility.

Published OnlineFirst November 22, 2013; DOI: 10.1158/0008-5472.CAN-13-1051

Grant Support

Funding for the iCOGS infrastructure came from: the European Community's Seventh Framework Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175; COGS), Cancer Research UK (C1287/A10118, C1287/A 10710, C12292/A11174, C5047/A8384, C5047/A15007, C5047/A10692), the NIH (CA128978) and Post-Cancer GWAS initiative (No. 1 U19 CA 148537—the GAME-ON initiative), the Department of Defence (W81XWH-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer, Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund.

The OCAC is supported by a grant from the Ovarian Cancer Research Fund thanks to donations by the family and friends of Kathryn Sladek Smith (PPD/RPCI.07). The scientific development and funding for this project were in part supported by the US National Cancer Institute GAME-ON Post-GWAS Initiative (U19-CA148112). This study made use of the data generated by the Wellcome Trust Case Control consortium. A full list of the investigators who contributed to the generation of the data is available at http://www.wtccc.org.uk/. Funding for the project was provided by the Wellcome Trust under award 076113.

B. Charbonneau is supported by R25 CA92049. G. Chenevix-Trench and P.A. Fasching are supported by the Deutsche Krebshilfe. B.Y. Karlan holds an American Cancer Society Early Detection Professorship (SIOP-06-258-01-COUN). L.E. Kelemen is supported by a Canadian Institutes of Health Research New Investigator award (MSH-87734).

Funding of the constituent studies was provided by the Minnesota Ovarian Cancer Alliance; the Mayo Foundation; the Fred C. and Katherine B. Andersen Foundation; the American Cancer Society (CRTG-00-196-01-CCE); the California Cancer Research Program (00-01389V-20170, N01-CN25403, 2II0200); the Canadian Institutes for Health Research (MOP-86727); Cancer Council Victoria; Cancer Council Queensland; Cancer Council New South Wales; Cancer Council South Australia; Cancer Council Tasmania; Cancer Foundation of Western Australia; the Cancer Institute of New Jersey; Cancer Research UK (C490/A6187, C490/A10119, C490/A10124, C536/A13086, C536/A6689); the Celma Mastry Ovarian Cancer Foundation the Danish Cancer Society (94-222-52); ELAN Funds of the University of Erlangen-Nuremberg; the Eve Appeal; the Helsinki University Central Hospital Research Fund; Sigrid Juselius Foundation; Imperial Experimental Cancer Research Centre (C1312/A15589); the Ovarian Cancer Research Fund; Nationaal Kankerplan of Belgium; the L & S Milken Foundation; the Polish Ministry of Science and Higher Education (4 PO5C 028 14, 2 PO5A 068 27); the Roswell Park Cancer Institute Alliance Foundation; the U.S. Army Medical Research and Materiel Command (W81XWH-07-1-0449); the U.S. National Cancer Institute (K07-CA80668, K07-CA095666, K07-CA143047, K22-CA138563, N01-CN55424, N01-PC067010, N01-PC035137, P01-CA017054, P01-CA087696, P30-CA072720, P50-CA105009, P50-CA136393, R01-CA014089, R01-CA016056, R01-CA017054, R01-CA049449, R01-CA050385, R01-CA054419, R01-CA058598, R01-CA058860, R01-CA061107, R01-CA061132, R01-CA063682, R01-CA064277, R01-CA067262, R01-CA071766, R01-CA074850, R01-CA076016, R01-CA080742, R01-CA080978, R01-CA087538, R01-CA092044, R01-095023, R01-CA106414, R01-CA122443, R01-CA112523, R01-CA114343, R01-CA126841, R01-CA149429, R03-CA113148, R03-CA115195, R37-CA070867, R37-CA70867, U01-CA069417, U01-CA071966, and Intramural research funds); NIH/National Center for Research Resources/General Clinical Research Center grant MO1-RR000056; the U.S. Army Medical Research and Material Command (DAMD17-98-1-8659, DAMD17-01-1-0729, DAMD17-02-1-0666, DAMD17-02-1-0669); the National Health and Medical Research Council of Australia (199600, 400281, 209057, 251533, 396414, 504715); the German Federal Ministry of Education and Research of Germany Programme of Clinical Biomedical Research (01 GB 9401); the state of Baden-Württembergthrough Medical Faculty of the University of Ulm (P.685); the Lon V. Smith Foundation (LVS-39420); the Oak Foundation; the OHSU Foundation; the Mermaid I project; the Rudolf-Bartling Foundation; the UK National Institute for Health Research Biomedical Research Centres at the University of Cambridge, Imperial College London, University College London Hospital and the Royal Marsden Hospital; WorkSafeBC; Helse Vest, The Norwegian Cancer Society, The Research Council of Norway (HBS/NOR).

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Received April 11, 2013; revised August 19, 2013; accepted September 27, 2013; published OnlineFirst November 22, 2013.

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Published OnlineFirst November 22, 2013; DOI: 10.1158/0008-5472.CAN-13-1051

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Risk of Ovarian Cancer and the NF-κB Pathway: Genetic Association with *IL1A* and *TNFSF10*

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Cancer Res 2014;74:852-861. Published OnlineFirst November 22, 2013.