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Article

Copy Number Variants Are Ovarian Cancer Risk Alleles at Known and Novel Risk Loci

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ARTICLE

Abstract

Background: Known risk alleles for epithelial ovarian cancer (EOC) account for approximately 40% of the heritability for EOC. Copy number variants (CNVs) have not been investigated as EOC risk alleles in a large population cohort. **Methods:** Single nucleotide polymorphism array data from 13 071 EOC cases and 17 306 controls of White European ancestry were used to identify CNVs associated with EOC risk using a rare admixture maximum likelihood test for gene burden and a by-probe ratio test. We performed enrichment analysis of CNVs at known EOC risk loci and functional biofeatures in ovarian cancer–related cell types. **Results:** We identified statistically significant risk associations with CNVs at known EOC risk genes; *BRCA1* ($P_{EOC} = 1.60E\text{-}21$; $OR_{EOC} = 8.24$), *RAD51C* ($P_{\text{high-grade serous ovarian cancer [HGSOC]}} = 5.5E\text{-}4$; odds ratio $[OR]_{HGSOC} = 5.74$ del), and *BRCA2* ($P_{HGSOC} = 7.0E\text{-}4$; $OR_{HGSOC} = 3.31$ deletion). Four suggestive associations ($P < .001$) were identified for rare CNVs. Risk-associated CNVs were enriched ($P < .05$) at known EOC risk loci identified by genome-wide association study. Noncoding CNVs were enriched in active promoters and insulators in EOC-related cell types. **Conclusions:** CNVs in *BRCA1* have been previously reported in smaller studies, but their observed frequency in this large population-based cohort, along with the CNVs observed at *BRCA2* and *RAD51C* gene loci in EOC cases, suggests that these CNVs are potentially pathogenic and may contribute to the spectrum of disease-causing mutations in these genes. CNVs are likely to occur in a wider set of susceptibility regions, with potential implications for clinical genetic testing and disease prevention.

Table 1. Study participant age and copy number variant distributions[a]

Statistical category	Controls (n = 17 306)	EOC cases (n = 13 071)	HGSOC cases (n = 8679)	P_{EOC}	P_{HGSOC}
Mean age (range)	56.1 (18-97)	58.9 (16-93)	60.1 (18-93)	<.001	<.001
CNV segments, No. (%)					
All	91 674	69 056	46 831	—	—
Deletions	46 637 (50.9)	35 165 (50.9)	23 900 (51.0)	—	—
Duplications	45 037 (49.1)	33 891 (49.1)	22 931 (49.0)	—	—
CNV segments, mean					
All	5.3	5.3	5.3	.59	.68
Deletions	2.7	2.7	2.7	.78	.83
Duplications	2.6	2.6	2.6	.63	.44
Median CNV length, kb					
All	22.2	21.9	21.4	.57	.91
Deletions	13.7	13.4	13.5	.68	.77
Duplications	37.1	36.7	36.1	.64	.87
Mean CNV length, kb					
All	67.4	67.8	67.3	.57	.91
Deletions	44.6	44.9	44.8	.68	.77
Duplications	91.0	91.6	90.8	.64	.87

[a]CNV = copy number variant; EOC = epithelial ovarian cancer; HGSOC = high-grade serous ovarian cancer.

Epithelial ovarian cancer (EOC) has a complex genetic architecture. Genetic risk alleles include highly penetrant pathogenic mutations in the *BRCA1* and *BRCA2* genes (1); rare mutations in moderately penetrant risk genes including *BRIP1*, *RAD51D*, *RAD51C*, *FANCM*, and *PALB2* (2-5); and many common, low-risk polymorphisms identified by genome-wide association studies (GWAS) (6-17). The lifetime risk for ovarian cancer is 1.4% in the general population of the United States, however, this is greatly increased in carriers of deleterious mutations in *BRCA1* and *BRCA2* (44% and 17% lifetime risk, respectively) (18). The presence of a *BRCA1* or *BRCA2* mutation remains the strongest genetic risk factor for predicting a woman's risk of EOC and is now routinely used to guide clinical interventions, including highly effective prevention by risk-reducing surgery. The genetic risk alleles for EOC identified so far account for approximately 40% of the heritability, suggesting there are many genetic risk alleles yet to be discovered (19).

The human genome harbors approximately 5000 to 10 000 structural variants (SVs), including deletions, duplications, insertions, and inversions, estimated to impact up to 13% of the human genome (20-22). By comparison, single nucleotide polymorphisms (SNPs) are estimated to affect approximately 0.1% of the human genome; thus, the estimated proportion of the human genome under structural variation is far higher than that due to SNPs. Despite this, copy number variants (CNVs; deletions and duplications) have not been analyzed at a similar scale as SNP variation, because of the cost of whole genome sequencing and technical challenges calling CNVs from genotyping arrays.

Previous studies have reported CNVs that contribute to the disease risk of other complex diseases such as breast cancer, pancreatic cancer, and diabetes (23-32). Similar extensive studies have not been performed in EOC cases, in part because of difficulty identifying large genotyped EOC case-control populations that can detect rare CNVs with sufficient power (33). Two previous genome-wide CNV analyses in approximately 1000 EOC cases and approximately 3000 unaffected controls failed to identify CNVs associated with disease risk or survival after multiple testing correction (34,35). In the current study, we have used genome-wide genotyping data from 13 071 EOC cases, including 8679 high-grade serous ovarian cancer (HGSOC) cases and 17 306 controls to identify CNVs throughout the genome and evaluate their associations with EOC risk.

Methods

Participants

The Ovarian Cancer Association Consortium (OCAC) collated and genotyped blood-derived DNA on the Illumina Infinium OncoArray as previously described (6). We selected 13 071 cases and 17 306 controls of White European ancestry from OCAC studies within countries with both cases and controls that passed genotyping quality control measures previously described (6). All participants signed an informed consent approved by the institutional review board of the recruiting institution. Demographics for these participants and their CNV distributions are listed in Supplementary Table 1 (available online) and Table 1.

CNV Calling Method

The CamCNV pipeline was used to call rare CNVs from the log R ratio (LRR) intensity measurements for each OncoArray probe (36). Principal component analysis adjustment was applied to the LRR for each OCAC study to mitigate the impact of technical batch effects. We excluded outlier probes based on LRR residual. Remaining CNV calls after additional quality control exclusions (see Supplementary Methods, available online) were lifted into hg38 from hg19 for downstream analysis, using University of California, Santa Cruz, Genome Browser liftOver.

Rare CNVs Association Analysis

A likelihood ratio test was performed to test for association with deletions or duplications at each probe where CNVs were observed in at least 0.05% of samples. For downstream enrichment analysis, we used probes covered by at least 5 CNVs (20 981 probes with deletions only, 30 917 with duplications only, and 5515 with deletions and duplications). Individual copy number variants were assigned the minimum *P* value of any probes they overlapped.

Gene burden analysis was performed by assigning probes to a single protein coding gene in the University of California, Santa Cruz, Genome Browser's knownGene table. Gene burden analyses were performed using the rare admixture maximum likelihood test (RAML) on genes with at least 5 samples carrying a CNV (37). The Bonferroni correction based on the number of genes tested in RAML for deletions, duplications, and both types of CNVs combined was a *P* value less than 6.37E-6 for all EOC and a *P* value less than 7.07E-6 for HGSOC. Because the smallest exact *P* value in our RAML analysis was a *P* value less than 1.0E-6, we additionally performed a binomial test using the frequencies of CNVs in cases and controls within BRCA1 to obtain a more precise *P* value.

GWAS and Transcriptome-Wide Association Study Enrichment Analysis

Enrichment of CNVs at known EOC risk loci was performed at known genome-wide statistically significant loci from the most recent GWAS of EOC and HGSOC (Coetzee S, Dareng EO, Peng P-C, Rosenow W, Tyrer JP, Chen S, et al, *In Review*) and genes identified by transcriptome-wide association (TWAS) studies by Gusev et al. (38) and Lu et al. (39). Analysis was performed twice; with CNVs overlapping BRCA1 included and then excluded. Genes at GWAS genome-wide statistically significant loci and TWAS genes (n = 37) were mapped to linkage disequilibrium (LD) blocks from the 1000 Genomes (1000G) European subpopulation (40) and CNVs intersecting these LD blocks retained for analysis. Enrichment was performed using a foreground of CNVs associated with EOC containing 1 or more probes with a *P* value less than .05 in association analyses. The foreground was used to generate a 1000-fold randomly selected background. Enrichment analysis was performed in R using FunciVar (41,42).

Functional Annotation and Noncoding Enrichment Analysis

Functional biofeatures for 18 cell lines related to ovarian cancer or with shared biological features of candidate precursor cell types (Supplementary Table 3, available online) were collated for enrichment analysis. Individual samples were processed and analyzed as previously described (42,43) and are described in detail in the Supplementary Methods (available online). Enrichment was performed with FunciVar (42), using a foreground of noncoding CNVs associated with EOC and/or HGSOC and a 1000-fold randomly selected set of regions as a background. Using these 2 lists, FunciVar then intersects each variant with functional annotations, which in this analysis were our ChromHMM states lifted into hg38. The significance of results is reported as probability that foreground variants have more overlaps with the functional annotation than background regions.

Common CNVs Tagged by SNPs

A list of SNPs in high LD (≥0.8) with common CNVs identified in 1000G (44) were looked up in the most recent EOC and HGSOC GWAS (Coetzee S, Dareng EO, Peng P-C, Rosenow W, Tyrer JP, Chen S, et al, *In Review*). We applied a Bonferroni threshold to identify CNV-tagging SNPs that were statistically significantly associated within the nonmucinous EOC GWAS analysis, which includes all invasive subtypes except for the mucinous histotype. SNPs were considered statistically significant with a *P* value less than 2.09E-6.

Results

Rare CNVs at Known EOC Susceptibility Gene Loci

We identified 160 730 CNV segments, with an average of 5.3 CNVs detected in each study participant. The median deletion size was 13.6 kb, and the median duplication size was 37.0 kb (Table 1). Rare CNVs retained for analysis ranged from 0.003% to 2.95% frequency (Table 1). More than 49% of deletions and 30% of duplications in our dataset overlapped (≥90% of length) with a rare CNV identified in women of European descent in the 1000G. Gene burden analysis was performed for all EOC cases and in HGSOC cases separately (Bonferroni corrected significance thresholds $P \leq$ 6.37E-6 and $P \leq$ 7.07E-6, respectively). In both analyses, the most statistically significant risk gene was *BRCA1* (P_{EOC} < 1.0E-6, odds ratio $[OR]_{EOC}$ = 8.24; P_{HGSOC} < 1.0E-6, OR_{HGSOC} = 7.29; Table 2; Supplementary Tables 4 and 5, available online). We identified 65 cases and 5 controls predicted to be hemizygous for a deletion, and 40 cases and 12 control participants with predicted duplications; 105 of 13 071 (0.80%) EOC cases, 93 of 8679 (1.1%) HGSOC cases, and 17 of 17 306 (0.098%) controls harbored a predicted deletion or duplication of *BRCA1* (*P* = 1.60E-21). Deletions and duplications at the *BRCA1* locus are illustrated in Figure 1, A. The most common CNV we found in *BRCA1* is a duplication at exon 13, a known relatively common CNV also called *BRCA1*-ins6kbEx13 described in Mazoyer et al. (45). This duplication is found in 20 cases and 0 controls. The most common deletion in BRCA1 in our data is found in exon 22, where a common deletion is known in families from the Netherlands (46). This was found in 10 cases, 5 of which are from the Netherlands (2.3% of all Netherlands cases have this specific CNV). The most common CNV in BRCA2 was a previously reported (47) deletion of exons 14-16, found in 4 cases in our study.

We found evidence of CNV EOC risk associations spanning 2 additional known ovarian cancer susceptibility gene regions: *RAD51C* (P_{EOC} = 7.0E-4, OR_{EOC} = 5.63; P_{HGSOC} = 4.33E-4, OR_{HGSOC} = 4.64) and *BRCA2* (deletions only; P_{EOC} = 0.0062, OR_{EOC} = 4.31; P_{HGSOC} = 7.0E-4, OR_{HGSOC} = 3.31; Table 2). Risk associations were stronger in HGSOC, consistent with previous studies of these genes (Table 2; Figure 1, B and C) (48,49). In addition, we found evidence of association for 12 genes not previously associated with EOC risk (*P* < .002; Table 2) including *PRKACG*, a cAMP-dependent protein kinase catalytic subunit gamma at 9q21.11 associated with a decreased risk in all EOC cases (*P* < EOC = 5.67E-4, OR_{EOC} = 0); the filamin-binding LIM protein 1 (*FBLIM1*) gene locus at 1p36.21 associated with increased risk in all EOC cases (P_{EOC} = 8.50E-4, OR_{EOC} = Not Available [NA]); and *ARHGAP24* at 4q21.23, where both deletions and duplication were associated with an increased risk for HGSOC (*P* = .00140, OR_{HGSOC} = 3.97; Table 2).

Rare CNV Association Analysis

To detect associations with individual CNVs, we restricted analyses to probes intersecting deletions or duplications with a frequency of at least 0.05% of samples (n = 16 for EOC, n = 13 for HGSOC). There were 6882 probes with deletions, and 9778 probes with duplications were analyzed. We identified 16 CNVs associated with risk for EOC or HGSOC (Table 3; Figure 2). Some individual deletions and duplications within *BRCA1* are frequent enough to appear in this analysis, and they are the only CNVs with *P* values below a significance threshold corrected for multiple testing. Outside of the *BRCA1* locus, the most statistically significant deletion falls within the long noncoding *LINC01194*

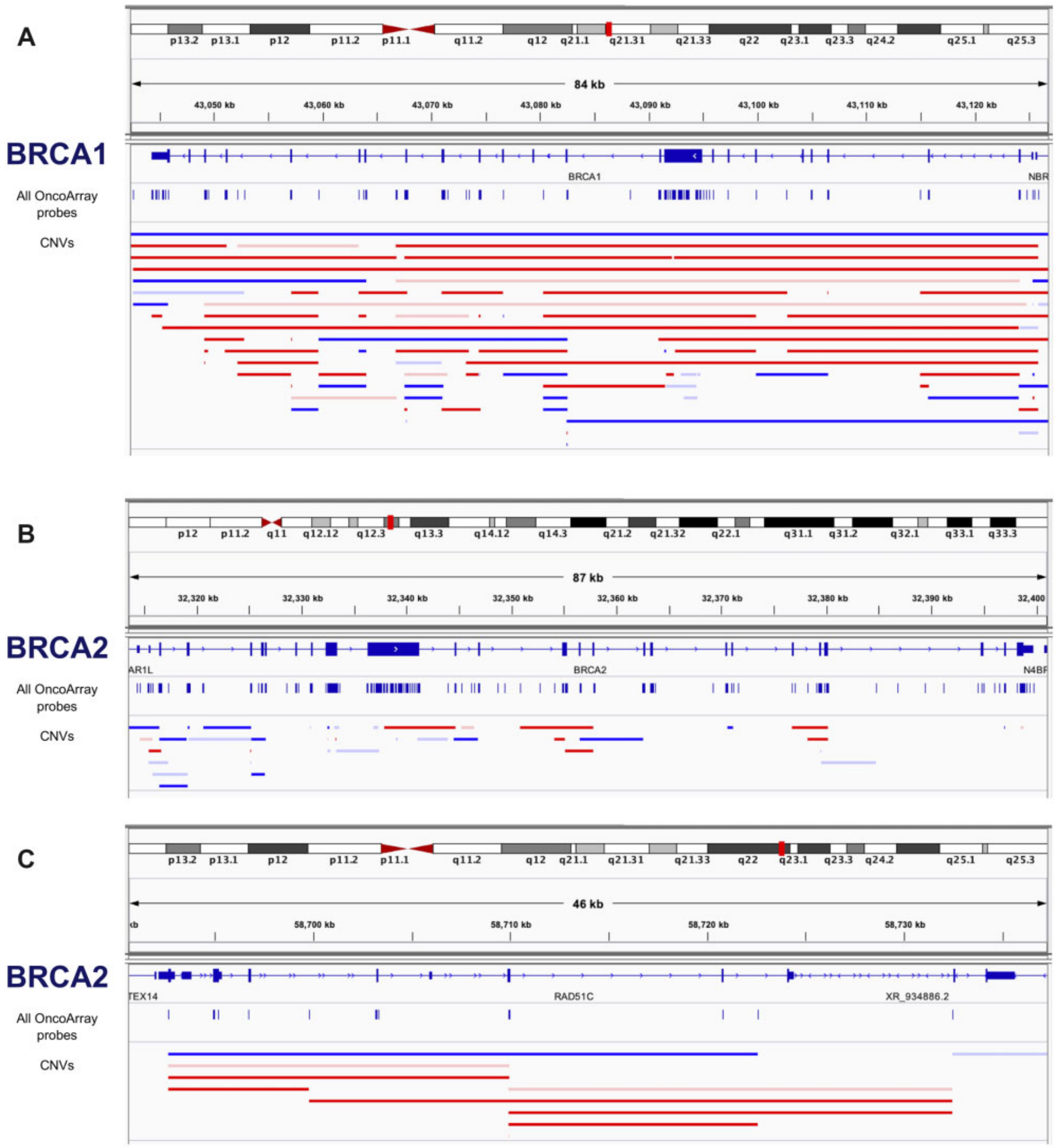

Figure 1. CNVs identified at the *BRCA1*, *BRCA2*, and *RAD51C* susceptibility gene risk loci in EOC cases and controls. CNVs of varying size predicting deletions (**horizontal red bars**) and duplications (**horizontal blue bars**) in EOC cases (**solid bars**) and controls (**faint bars**) at the **(A)** *BRCA1*, **(B)** *BRCA2*, and **(C)** *RAD51C* gene loci. The location of all probes genotyped on the Illumina OncoArray and used to "call" copy number variations are shown as **vertical blue lines**. CNV = copy number variants.

also known as Cancer Testis Antigen 49 (n = 137; $P = .0007$). The strongest novel duplication result (n = 90; $P = .0003$) falls within the seventh intron of the *DCDC2* gene.

CNV Enrichment at Risk Loci Identified by GWAS and TWAS

Statistically significant CNVs intersected LD blocks at EOC GWAS risk regions at 7 of 27 EOC risk loci, even when *BRCA1* CNVs were excluded ($P < .05$; Table 4; Supplementary Tables 8 and 9, available online). HGSOC histotype-specific GWAS regions were also statistically significantly enriched for risk CNVs; statistically significant CNVs intersected 12 of 30 loci ($P < .05$; Table 4; Supplementary Table 8, available online). GWAS risk regions with a statistically significant enrichment for CNVs intersected both known and potentially novel causal genes. CNVs identified in all EOC cases were statistically significantly enriched within the bodies of TWAS genes in EOC but not HGSOC (Supplementary Table 9, available online), and the regions defined by LD blocks around the same TWAS genes were not statistically significantly enriched for CNVs in either EOC or HGSOC.

EOC Risk Associations for Common CNVs

To identify common CNVs associated with EOC and HGSOC risk, we used tag SNPs ($r^2 > 0.8$) for common CNVs in participants of European descent (>1% frequency). We evaluated 23 960 SNPs tagging 3681 CNVs in the largest GWAS dataset for EOC and HGSOC risk (Supplementary Table 10, available online). We identified 4 statistically significant SNPs tagging 4 CNVs at 2 loci ($P < 2.09E-6$) in both the EOC (excludes mucinous EOC) and the HGSOC histotype–specific GWAS (Figure 2, Table 5). At 9p22.2, the risk-associated

Table 2. Gene burden testing results for rare CNVs in all EOC or HGSOC cases with a P value less than .002

Gene	No. of cases	No. of HGSOC	No. of controls	OR_{EOC}	OR_{HGSOC}	CNV type[a]	All cases P	HGSOC cases P
BRCA1	40	35	12	4.42	3.87	Duplication	<1.00E-06	<1.00E-06
BRCA1	65	58	5	17.29	15.42	Deletion	<1.00E-06	<1.00E-06
RAD51C	17	14	4	5.63	4.64	Both	7.00E-04	4.33E-04
RAD51C	14	13	3	6.18	5.74	Deletion	6.00E-03	5.50E-04
PRKACG	0	0	15	0.00	0.00	Duplication	5.67E-04	9.00E-03
BRCA2	13	10	4	4.31	3.31	Deletion	6.20E-03	7.00E-04
FBLIM1	11	6	0	NA	NA	Deletion	8.50E-04	4.80E-03
HAS3	12	10	5	3.18	2.65	Duplication	1.13E-02	1.20E-03
ARHGAP24	12	9	3	5.30	3.97	Both	1.39E-02	1.40E-03
LSP1	35	27	20	2.32	1.79	Both	2.41E-02	1.40E-03
SNX29	8	5	1	10.60	6.62	Duplication	1.40E-03	7.70E-03
PIP5K1B	1	0	20	0.07	0.00	Both	1.53E-03	2.73E-02
ALKBH4	6	2	0	NA	NA	Duplication	1.65E-03	NA
LRWD1	6	2	0	NA	NA	Duplication	1.65E-03	NA
LSP1	33	26	17	2.57	2.03	Duplication	2.31E-02	1.70E-03
TTLL2	8	3	1	10.60	3.97	Duplication	1.80E-03	3.29E-02
NAT1	8	6	2	5.30	3.97	Deletion	1.90E-03	6.00E-03

[a]Combined duplications and deletions P value result included only if it was more statistically significant than deletions or duplications alone. CNV = copy number variant; EOC = epithelial ovarian cancer; HGSOC = high-grade serous ovarian cancer; OR = odds ratio; NA = Not Available.

Table 3. CNVs statistically significantly associated with EOC and HGSOC with a P value less than .005

Chr	CNV region start	CNV region end	Type	No. sig probes	Probe location	OR_{EOC}	P_{EOC}	EOC Carrier count	OR_{HGSOC}	P_{HGSOC}	HGSOC carrier count
17	43 080 276	43 082 575	Duplication	7	*BRCA1* coding	NA[a]	9.72E-10	26	NA[a]	1.02E-11	23
17	43 049 093	43 125 836	Deletion	6	*BRCA1* coding	28.6	2.57E-07	20	33.22	5.38E-07	16
6	24 221 271	24 221 660	Duplication	3	*DCDC2* intronic	0.45	3.65E-04	90	0.53	9.69E-03	84
5	12 692 574	12 726 378	Deletion	7	*LINC01194* LncRNA	0.53	7.22E-04	137	0.59	9.90E-03	126
9	69 064 550	69 225 129	Duplication	6	*FXN*, *TJP2* coding	0.19	1.48E-03	24	0.19	5.51E-03	23
17	1 197 175	1 198 288	Deletion	4	*ABR* intronic	0.62	2.50E-03	188	0.63	9.71E-03	168
9	116 713 991	116 729 732	Deletion	4	*ASTN2* coding	3.53	2.55E-03	26	3.36	9.74E-03	19
23	67 910 806	67 923 215	Duplication	3	Intergenic	2.7	3.38E-03	40	2.32	3.07E-02	30
11	1 841 637	1 886 457	Duplication	5	*LSP1* intronic	2.46	4.66E-03	44	3.1	7.68E-04	31
2	50 669 275	50 697 220	Deletion	5	*NRXN1* intronic	2.93	5.14E-03	30	3.32	3.74E-03	25
12	115 341 220	115 341 234	Deletion	3	Intergenic	0.3	6.58E-03	28	0.18	3.11E-03	25
10	82 776 430	82 797 323	Deletion	4	*NRG3* intronic	3.91	7.09E-03	21	4.44	4.33E-03	18
9	12 350 523	12 443 586	Deletion	11	Intergenic	2.33	1.14E-02	40	3.01	1.68E-03	36
23	36 457 791	36 541 981	Duplication	4	Intergenic	0.38	1.23E-02	34	0.15	8.57E-04	28
6	168 031 413	168 196 562	Duplication	37	*KIF25*, *FRMD1*	0.85	3.81E-02	753	0.76	1.93E-03	628
1	195 862 228	195 905 802	Deletion	10	Intergenic	1.43	5.66E-02	119	1.83	2.18E-03	110

[a]NA: This deletion was only observed in cases; odds ratio (OR) could not be calculated. CNV = copy number variant; EOC = epithelial ovarian cancer; HGSOC = high-grade serous ovarian cancer.

CNV lies between *BNC2* and *CNTLN*, intersecting the promoter of a long noncoding RNA and the previously identified risk SNPs for EOC (50). The CNVs at 17q21.31 are within a common inversion polymorphism also associated with a microdeletion syndrome and predicted to disrupt *LINC02210-CRHR1*, *MAPT*, and *KANSL1* (51,52).

CNVs Are Enriched in Active Regulatory Elements in Ovarian Cancer–Related Cell Types

We identified 1707 and 1948 CNVs within nonprotein-coding DNA regions associated with EOC or HGSOC risk, respectively ($P < .05$; Supplementary Tables 6 and 7, available online). We evaluated the enrichment of these CNVs in chromatin states (weak promoter, active promoter, active region, active enhancer, weak enhancer, insulator, and transcribed) mapped in 18 ovarian cancer–related cell types (Supplementary Table 3, available online) (Plummer JT, Dezem FS, Davis B, Chen S, Seo J-H, Giambartolomei C et al, *In Review*). We identified statistically significant enrichment of EOC risk CNVs in insulators and modest enrichment at weak promoters (Figure 3); depletion in active promoters; and enhancers (Supplementary Figure 1, Supplementary Table 11, available online). Restricting the analysis to HGSOC risk CNVs to HGSOC showed a similar pattern of enrichment (Supplementary Figure 2, available online).

Discussion

In this study, we used genome-wide genotype array probe signal intensity data for more than 13 000 EOC cases and more than

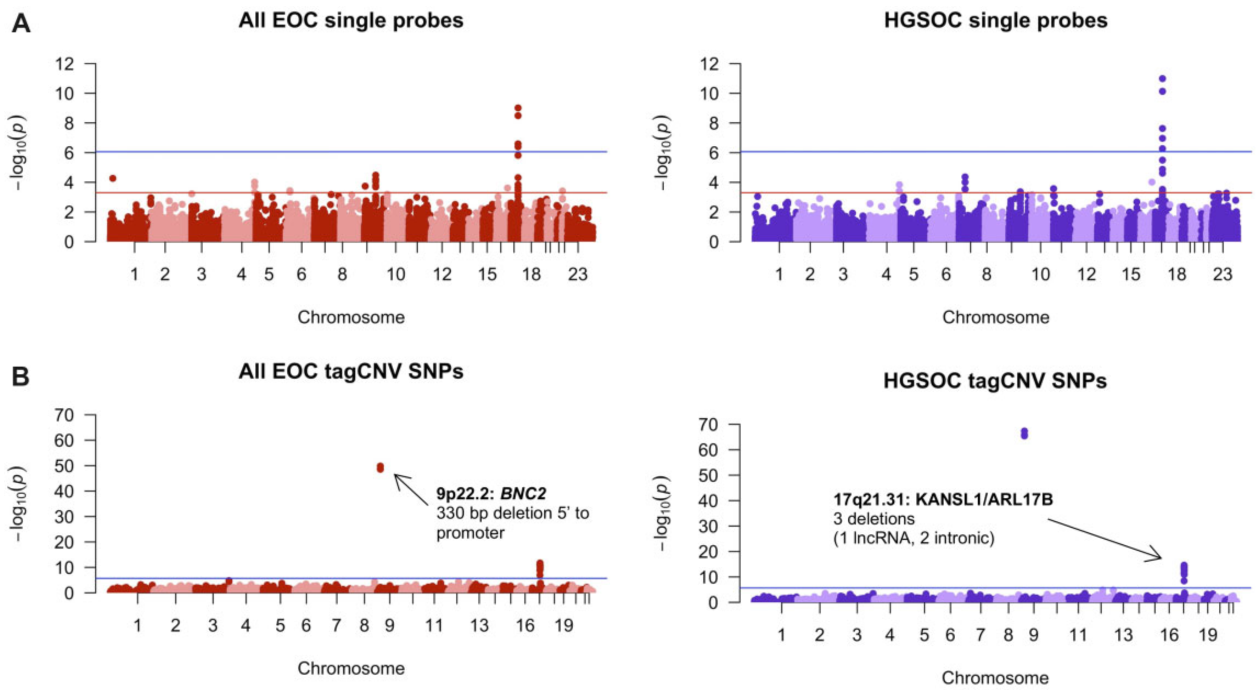

Figure 2. A) Manhattan plots showing the results of single-probe CNV association testing. At a Bonferroni P value cutoff (**blue line**) of $P < 8.71E\text{-}7$ for the all EOC cases (based on 57 432 tests) and $P < 8.56E\text{-}7$ for HGSOC cases only (based on 58 382 tests) identified statistically significant probes at the BRCA1 gene locus. Evidence of several additional risk associations with a Bonferroni P value cutoff of $P < 5E\text{-}4$, including associations at intergenic sites, are also shown. **B)** Manhattan plot displaying results of common CNV analysis. At a Bonferroni P value cutoff of $P < 2.09E\text{-}6$ based on 23 960 tag SNPs included in the lookup, we identified statistically significant SNPs at 4 loci. At these loci, there are common CNVs in high linkage disequilibrium with GWAS SNPs that may account for some of the variation leading to differences in risk at that SNP. CNV = copy number variants; EOC = epithelial ovarian cancer; GWAS = genome-wide association studies; HGSOC = high-grade serous ovarian cancer; SNP = single nucleotide variants.

Table 4. GWAS loci with CNVs associated with EOC or HGSOC risk ($P < .05$)

Cytoband	rsID	GWAS P	LD block start	LD block end
NMOC loci				
3q28	rs9869209	6.61E-09	190508818	192626025
5p15.33	rs4449583	2.76E-21	982137	2132328
10p12.31	rs7084454	1.86E-12	19427949	22483354
17q21.31[a]	rs146596949	1.26E-51	41743558	43694719
17q21.31[a]	rs575499584	4.12E-18	44979537	47798656
17q21.32	rs12946636	9.92E-25	47798656	49440038
19p13.11	rs4808075	5.76E-26	16263605	18299052
HGSOC associated loci				
4q13.2/4q13.3	rs4149419	2.66E-08	67989047	70183435
5p15.33	rs4449583	1.09E-19	982137	2132328
9q31.1	rs2122577	2.94E-09	103205694	104819468
9p22.1/9p21.3	rs7851336	2.54E-10	18661053	20463536
10p12.31	rs7084454	1.48E-09	19427949	22483354
13q13.1	rs11571815	4.32E-09	31727678	33202766
15q26.1	rs76119208	3.36E-09	89932319	91621162
17q12	rs11657964	2.63E-12	36141651	38653091
17q21.31	rs146596949	3.11E-56	41743558	43694719
17q21.31	rs575499584	1.69E-19	44979537	47798656
17q21.32	rs12946636	5.54E-19	47798656	49440038
19p13.11	rs56069439	8.41E-38	16263605	18299052

[a]BRCA1 locus. CNV = copy number variants; GWAS = genome-wide association analysis; LD = linkage disequilibrium; HGSOC = high-grade serous ovarian cancer; NMOC = all nonmucinous ovarian cancer.

17 000 controls to characterize CNVs and evaluate their associations with EOC and HGSOC risk. This study represents the largest to evaluate the contribution of CNVs to ovarian cancer risk performed to date. Two previous studies failed to find strong evidence of CNVs associated with EOC risk (34,35). Both prior studies focused on common CNVs (>1% frequency), whereas we focused

Table 5. HRC tagSNPs in LD with known common CNVs from 1000G that are statistically significantly associated with EOC risk (hg38)[a]

tagSNP	Chr	Position	Effect allele	Noneffect allele	CNV start	CNV end	CNV type	Length (bp)	P_{NMOC}	No. sig tagSNPs	P_{HGSOC}	No. sig tagSNPs
rs10962691	9	16915107	G	C	16905594	16905924	Deletion	330	1.48E-50	3	4.38E-68	3
rs17689104	17	45705126	G	A	45753354	45753478	Deletion	124	3.12E-12	152	9.59E-15	152
rs17688922	17	45701985	A	G	45753354	45753478	Deletion	124	3.17E-12	152	9.55E-15	152
rs8080583	17	46085231	A	C	46009357	46009595	Deletion	238	1.85E-12	179	2.32E-15	181
rs8080583	17	46085231	A	C	46146541	46146855	Deletion	314	1.85E-12	179	2.32E-15	181

[a]1000G = 1000 Genomes project; CNV = copy number variant; EOC = epithelial ovarian cancer; HGSOC = high-grade serous ovarian cancer; HRC = Haplotype Reference Consortium; LD = linkage disequilibrium; NMOC = all nonmucinous ovarian cancer; SNP = single nucleotide polymorphism.

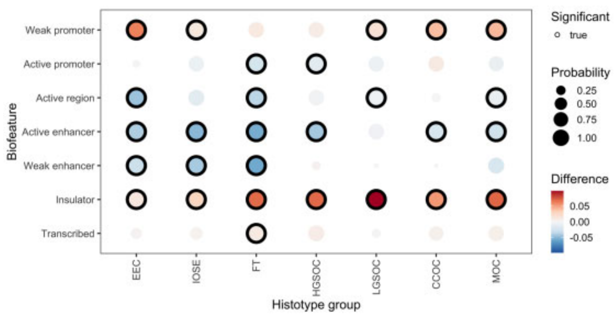

Figure 3. Enrichment of EOC statistically significant CNVs ($P < .05$) in functional biofeatures in ovarian cancer–related cell types. EOC risk CNVs are statistically significantly enriched in insulators across all ovarian cancer–relevant histotype consensus groups. The total number of risk CNVs in each biofeature per histotype grouping can be found in Supplementary Table 11 (available online). Abbreviations for histotypes are as follows: CCOC = clear cell ovarian cancer; EEC = endometriosis (precursor cell type); FT = fallopian tube secretory epithelial cells (precursor cell type); HGSOC = high-grade serous ovarian cancer; IOSE = immortalized ovarian surface epithelium (precursor cell type); LGSOC = low-grade serous ovarian cancer; MOC = mucinous ovarian cancer. CNV = copy number variants; EOC = epithelial ovarian cancer.

on rare CNVs, and this, along with the large difference in sample size, likely contributed to the lack of replication. Using gene burden analyses, we identified highly statistically significant deletions and duplications at the *BRCA1* gene locus and confirmed these findings using single probe association testing. We also found evidence of CNV risk associations at 2 other EOC susceptibility loci: *RAD51C* and *BRCA2*. A subset of EOC cases and controls included in this study have been previously sequenced to identify germline BRCA1 (n = 89), *BRCA2* (n = 106), and *RAD51C* (n = 8) coding variants (48,49,53), and none of the 203 patients carrying a pathogenic mutation in any of these genes also harbored a predicted CNV in these genes. As single nucleotide variants (SNVs) and CNVs are rare in these genes, we expect patients with concurrent pathogenic SNVs and CNVs to be extremely rare. For all 3 loci, EOC risk estimates were stronger when we restricted the analyses to HGSOC cases only, consistent with previous studies indicating that mutations in these genes are more strongly associated with HGSOC.

Prior studies report pathogenic *BRCA1* coding sequence mutations at a frequency of 5.3% in HGSOC (48), and we identified CNVs at the *BRCA1* gene locus in 1.1% of HGSOC cases, suggesting CNVs represent a substantial contribution to the overall prevalence of *BRCA1* mutations in HGSOC cases. Previous candidate studies identified pathogenic deletions and rearrangements involving *BRCA1*, *BRCA2*, and moderate-risk CNVs in high-risk hereditary breast and ovarian cancer (HBOC) families where a mutation was not identified in clinical testing (54-61), and we identified deletions and duplications overlapping previously reported CNVs, such as deletions in exon 2-9 of *RAD51C* or deletions in exons 14-16 of *BRCA2* (55,57). *BRCA2* CNV mutations are rarer than *BRCA1* CNVs, however, they are still estimated to account for up to 8% of germline *BRCA2* mutations (47,62-67). The contribution of CNVs to *BRCA1* varies greatly depending on population, with CNVs being 3% of *BRCA1* mutations in South African HBOC families (68) and 27%-36% of *BRCA1* mutations in Dutch HBOC families (46,69). CNVs account for a smaller proportion of *BRCA2* carriers comparatively, with a Danish study of HBOC families finding *BRCA1* CNVs in 12.5% of all *BRCA1* carriers but only 2% of *BRCA2* carriers (62). Most estimates of contribution are from screening individuals in hereditary breast and ovarian cancer families rather than all ovarian cancer cases, as in our study, which may partially account for the fewer CNVs seen in our data. It is likely that *BRCA2* and *RAD51C* contain clinically relevant CNVs but also that other moderate-risk genes with CNVs or structural variants would be found in a cohort with sufficient sample size and a sensitive detection method. It is more difficult to find estimates of CNV contribution to these genes in nonfamilial studies. In a study of 376 000 participants undergoing genetic testing, 12.7% of pathogenic variants in *BRCA1*, 1.9% of pathogenic variants in *BRCA2*, and 21.1% of pathogenic variants in RAD51C were large rearrangements (70). The percent of all ovarian cancer patients with a CNV vs SNV as their pathogenic mutation in these genes is not currently available.

CNV association analyses also identified novel candidate ovarian cancer susceptibility genes, including *FBLIM1*, *HAS3*, and *LSP1*. Germline whole-exome sequencing studies have previously implicated *FBLIM1* as a putative susceptibility gene in HGSOC (71). The gene is differentially expressed between benign and malignant murine ovarian surface epithelial cells and is dysregulated in ovarian cancers (72,73). LSP1 is a candidate breast cancer susceptibility gene and may interact multiplicatively to increase breast cancer risk for BRCA2 mutation carriers (16,74-76), and the *HAS3* gene may also be associated with the development of chemoresistant ovarian cancer (77,78).

Rare variant association analysis detected a number of suggestive associations for individual variants. Only the *BRCA1* variants with large effect sizes (OR > 10) passed the multiple-testing *P* value threshold. If associations for rare CNVs are to be confirmed, a key question is the magnitude of effect sizes we should expect for CNVs outside the known genes. Sample size requirements scale linearly with decreasing minor allele frequence but quadratically for decreasing odds ratios (1/|[OR - 1]) (79). When compared with associations for common noncoding SNPs, the possible associations in this analysis have large odds ratios ranging from 0.15 to 0.76 and from 1.83 to 4.44. It is plausible that evolutionary younger rare variants not yet removed by negative selection can have a stronger biological effect than older common variants.

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There is also some evidence from sequencing studies that noncoding SVs such as CNVs are more likely to have a stronger biological effect than SNVs. For example, Abel et al. (80) calculated that each individual carried 122 rare variants (63% SNVs, 20% indels, 17% SVs) predicted to be deleterious, and given their relative frequency, SVs are 841-fold more likely to be deleterious than rare SNVs and 341-fold more than rare indels. We estimate that the probe coverage on the OncoArray allows us to detect up to 10% of the deletions and 25% of the duplications identified by the 1000G in the 0.05% to 1% frequency range in the European population.

The most statistically significantly risk-associated deletion impacts part of the long noncoding RNA *LINC01194* (n = 137, OR = 0.53; *P* = .0007). There is some evidence for an oncogenic role for *LINC01194* from expression analyses in colorectal tumors (81) and prostate tumors and cancer cell lines (82).The strongest duplication association was observed in an intron at the start of the *DCDC2* gene (n = 90, OR = 0.45; *P* = .0004). Interestingly, the reverse strand of this gene encodes *KAAG1*, which has been identified as an antigen expressed on the surface of cancer cells in a high proportion of ovarian tumors (83). The strongest result in the HGSOC analysis is for a duplication covering the first exon of the *LSP1* gene (n = 37, OR = 3.10; *P* = .0008) (71).

We observed enrichment of risk-associated CNVs at EOC risk loci identified by GWAS. A wide variety of genetic variation, including SNVs and CNVs at GWAS loci, may contribute cumulatively to observed signal through aggregation by LD, and CNV analysis may implicate candidate genes for further functional analysis. Most EOC-risk associated variants identified by GWAS lie in noncoding DNA regions. In our study, noncoding risk-associated CNVs were enriched in weak promoters and insulators (bound CTCF motifs), suggesting they mediate gene expression through their interaction with regulatory elements and the 3-dimensional structure of the genome. Studies have shown germline risk variants and CNVs altering CTCF sites underlie some human diseases (84,85).

We have used genome-wide analysis to identify rare CNVs associated with ovarian cancer risk, including at known EOC susceptibility gene loci *BRCA1*, *BRCA2*, and *RAD51C*. Given the frequency at which we detected these CNVs, it may be appropriate to expand the content of genetic risk assessment panels for breast and ovarian cancer to universally include coverage of CNVs at *BRCA1*, *BRCA2*, and *RAD51C* as likely pathogenic variants where such testing is not already standard (86). CNVs likely represent a missing fraction of heritability for ovarian cancer at known susceptibility genes and as independent risk variants. Evaluating the frequency of CNVs in larger EOC case-control populations and with whole genome sequencing on a population scale is warranted to improve our understanding of the genetic architecture for EOC.

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Notes

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Data Availability

All data used and code developed for these analyses are available on Github at https://github.com/Jones-Lab-CSMC/OCAC-Oncoarray-CamCNV.

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