Abstract #1287

Multigene Panel Testing and Risk Estimates in 10,233 Ovarian Cancer Cases

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Background

- *BRCA1* and *BRCA2* mutations are found in 10-15% of unselected OC cases and up to 40% of heritable OC cases
- Other genes including *BRIP1*, *RAD51C*, and *RAD51D*, have been associated with OC risk but magnitude of risk is less well defined
- OC is an established feature of Lynch syndrome, but the relative contributions of the MMR genes in OC is less clear
- Previous studies have been limited by:
  - Sample sizes large enough to estimate precise risks
  - Limited number of genes examined

Methods

Study population

- 10,233 ovarian cancer cases were referred to Ambry Genetics (Aliso Viejo, CA) for multigene panel testing between March 2012 and June 2016
- Analysis dataset is limited to Caucasian OC cases and ExAC non-Finnish European (excluding TCGA) controls

Multigene panel testing

- Targeted custom captures and sequencing along with targeted chromosomal microarray analysis[1]
- Results from 20 genes across 9 available multigene panels were evaluated

Statistical analyses

- Variants were classified as pathogenic or very likely pathogenic (P/VLP) in cases and ExAC controls using a 5-tier system
- Ambry cases were normalized to ExAC controls by removing LGRs and variants in the PMS2 pseudogene region from the analysis
- Standardized risk ratios (SRR) were calculated using observed frequency of P/VLP variants in Ambry OC cases and summed frequency of all P/VLP variants in ExAC
- Odds ratios for the case-case analysis were calculated using observed frequency of P/VLP variants in Ambry OC cases

Table 1. Characteristics of OC Cases

	All Ovarian Cancer Cases		Caucasian Analysis Subset	
	n	%	n	%
Total patients	10233		7768	
Ovarian cancer--Age at Diagnosis				
<40	1144	0.112	748	0.096
40-49	1701	0.166	1192	0.153
50-59	2885	0.282	2192	0.282
60-69	2705	0.264	2163	0.278
70-79	1364	0.133	1128	0.145
≥80	337	0.033	273	0.035
Unknown	97	0.009	72	0.009
Personal History of Other Cancers*+	2564	0.251	1992	0.256
Breast	1366	0.533	1073	0.539
Colorectal	191	0.074	142	0.071
Pancreatic	42	0.016	34	0.017
Endometrial	658	0.257	503	0.253
Other	678	0.264	529	0.266
Family History of Cancer*^	8641	0.844	6710	0.864
Breast	4275	0.495	3404	0.507
Ovarian	1396	0.162	1068	0.159
Colorectal	2584	0.299	2084	0.311
Pancreatic	869	0.101	687	0.102
Endometrial	771	0.089	590	0.088

*Categories are not mutually exclusive
+ Categories use total number of patients reporting any personal history of non-ovarian cancer to calculate percentage
^ Categories use total number of patients reporting any family history of cancer to calculate percentage

Genes evaluated: *APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, CHEK2, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, TP53*

Table 3. Ovarian cancer case-case analysis by age at diagnosis

	Cases <60 at diagnosis n=4132			Cases ≥ 60 at diagnosis n=3564					
Gene	**Case AC**	**Case AF**	**Case AN**	**Case AC**	**Case AF**	**Case AN**	**OR**	**95%CI**	**p-value**
ATM	34	0.00509	6682	19	0.00326	5832	1.56	1.08-2.18	0.0182
BRCA1	226	0.02805	7950	70	0.01014	6902	2.91	2.20-3.90	$2.00x10^{-46}$
BRCA2	121	0.01509	7950	129	0.01869	6902	0.81	0.67-0.97	0.0140
BRIP1	19	0.00285	6660	42	0.00705	5812	0.4	0.24-0.63	$2.44x10^{-6}$
MSH2	25	0.00318	7856	3	0.00044	6842	7.26	4.70-10.71	$1.27x10^{-13}$
MSH6	43	0.00547	7856	5	0.00073	6842	7.56	3.00-24.50	$3.00x10^{-14}$
NBN	13	0.0018	6660	11	0.00172	5812	1.05	0.54-1.83	0.9507
PALB2	10	0.00149	6700	13	0.00222	5858	0.67	0.32-1.24	0.1485
RAD51C	29	0.00435	6660	21	0.00361	5812	1.21	0.81-1.73	0.3620
RAD51D	5	0.00083	6040	13	0.00243	5350	0.34	0.11-0.80	0.0022
TP53	5	0.00061	8264	10	0.0014	7128	0.43	0.14-1.01	0.0202

Figure 1. Percentage of P/VLP variants in genes associated with OC

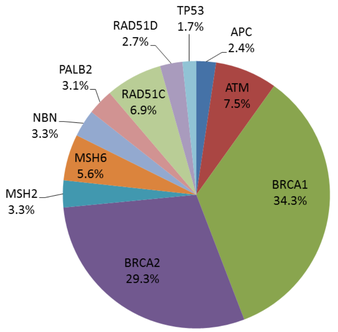

Table 2. SRR Risk Analysis: OC Cases compared to ExAC Controls^

	ExAC Controls*	All Caucasian OC Cases (n=7768)						Personal/Family Hx of CRC Removed (n=5950)						Personal/Family Hx of BC Removed (n=3830)					
Gene	**Control AF**	**Case AC**	**Case AN**	**Case AF**	**SRR**	**95% CI**	**p-value**	**Case AC**	**Case AN**	**Case AF**	**SRR**	**95% CI**	**p-value**	**Case AC**	**Case AN**	**Case AF**	**SRR**	**95% CI**	**p-value**
APC	0.00023	4	2920	0.00137	5.89	1.61-15.09	0.0103	2	1892	0.00106	4.55	0.55-16.42	0.1451	2	1212	0.00165	7.08	0.86-25.64	0.0660
ATM	0.00190	54	12630	0.00428	2.25	1.69-2.94	$1.84x10^{-7}$	36	9232	0.00390	2.06	1.44-2.85	0.0001	28	6118	0.00458	2.41	1.60-3.49	$6.33x10^{-5}$
BRCA1	0.00152	269	14978	0.01796	11.78	10.42-13.28	$3.50x10^{-182}$	190	10824	0.01755	11.52	9.94-13.28	$2.30x10^{-127}$	90	7448	0.01208	7.93	6.38-9.75	$1.00x10^{-47}$
BRCA2	0.00210	250	14978	0.01669	7.96	7.00-9.01	$2.30x10^{-99}$	189	10824	0.01746	8.33	7.18-9.60	$1.30x10^{102}$	103	7448	0.01383	6.6	5.38-8.00	$8.90x10^{-60}$
BRIP1	0.00092	58	12588	0.00461	4.99	3.79-6.45	$2.90x10^{-21}$	45	9200	0.00489	5.3	3.87-7.09	$1.30x10^{-17}$	23	6104	0.00377	4.08	2.59-6.13	$6.67x10^{-8}$
MSH2	0.00011	23	14822	0.00155	13.91	8.82-20.87	$2.50x10^{-17}$	9	10576	0.00085	7.63	3.49-14.48	$8.49x10^{-6}$	6	7488	0.00080	7.18	2.64-15.63	0.0004
MSH6	0.00063	47	14822	0.00317	5.04	3.70-6.70	$1.70x10^{-17}$	20	10576	0.00189	3	1.83-4.64	$4.50x10^{-5}$	17	7488	0.00227	3.61	2.10-5.77	$1.91x10^{-5}$
NBN	0.00086	22	12588	0.00175	2.03	1.27-3.08	0.0037	13	9200	0.00141	1.64	0.88-2.81	0.1188	9	6104	0.00147	1.72	0.78-3.26	0.1706
PALB2	0.00056	22	12674	0.00174	3.08	1.93-4.67	$1.22x10^{-5}$	15	9270	0.00162	2.87	1.61-4.74	0.0007	4	6128	0.00065	1.16	0.32-2.97	0.9059
RAD51C	0.00068	44	12588	0.0035	5.12	3.72-6.88	$1.10x10^{-16}$	29	9200	0.00315	4.62	3.09-6.64	$7.30x10^{-11}$	20	6104	0.00328	4.8	2.93-7.42	$3.91x10^{-8}$
RAD51D	0.00015	11	11486	0.00096	6.34	3.16-11.34	$4.44x10^{-6}$	9	8478	0.00106	7.02	3.21-13.34	$1.63x10^{-5}$	6	5658	0.00106	7.02	2.58-15.27	0.0005
TP53	0.00034	15	15536	0.00097	2.87	1.61-4.74	0.0007	12	11180	0.00107	3.2	1.65-5.58	$1.07x10^{-3}$	5	7660	0.00065	1.94	0.63-4.54	0.2375

*ExAC control AF used to calculate SRR, 95% CI, and p-value for all analyses
^Results show n for genes that showed significant association with OC

Results

- High-risk associations (SRR>4.0) for known OC genes: *BRCA1*, *BRCA2*, *BRIP1*, *MSH2*, *MSH6*, *RAD51C*, and *RAD51D*
- Moderate-risk associations (SRR=2.0-4.0) for suspected OC genes: *ATM* and *PALB2*
- Attenuation of risks in sensitivity analyses:
  - PALB2 following removal of cases with breast cancer history
  - MSH2 and MSH6 following removal of cases with colorectal cancer history
- Associations with age at diagnosis::
  - <60: *ATM*, *BRCA1*, *MSH2*, and *MSH6,*
  - ≥60: *BRIP1* and *RAD51D*
- No significant associations with: *BARD1*, *CDH1* (AC=0), *CDKN2A* (AC=1), *CHEK2*, *MLH1*, *MRE11A*, *MUTYH*, *PMS2*, or *RAD50*
- Results not shown for *PTEN* (AC=10) due to low number of events in ExAC population

Conclusions

- We confirmed associations with OC risk for several known and suspected OC genes
- These finding shed light on the current NCCN guidelines for Lynch syndrome mutation carriers as no association with OC was identified for *MLH1* and *PMS2*
- We provide more precise estimates than previously reported for genes including *RAD51C* and *RAD51D*
- We did not find a significant association *BARD1* which is a previously suspected OC gene

References

1. LaDuca H, Stuenkel AJ, Dolinsky JS, et al: Utilization of multigene panels in hereditary cancer predisposition testing: analysis of more than 2,000 patients. Genet Med 16:830-7, 2014