Ambry Genetics®

Frequency of Germline Mutations in *BRIP1*, *RAD51C*, and *RAD51D* Among Women with Ovarian, Primary Peritoneal, and Fallopian Tube Cancer

Tara Namey, MS, LCGC; Holly LaDuca, MS, CGC; Bryan Mak, BS; Michelle Jackson, MS, CGC

Acknowledgements: Patrick Reineke & Andrew Castillo

BACKGROUND

- The National Comprehensive Cancer Network (NCCN) recently established guidelines to consider/recommend risk-reducing bilateral salpingo-oophorectomy in women who harbor germline mutations in *BRIP1*, *RAD51C*, and *RAD51D*.
- Our aim is to determine the frequency of pathogenic germline mutations in these genes among women with ovarian cancer referred for hereditary cancer multigene panel testing (MGPT).

Gene	Ovarian Cancer Risk	Reference(s)
BRIP1	up to 9%	#2
RAD51C	5-9%	#3; #4
RAD51D	10-12%	#3; #5

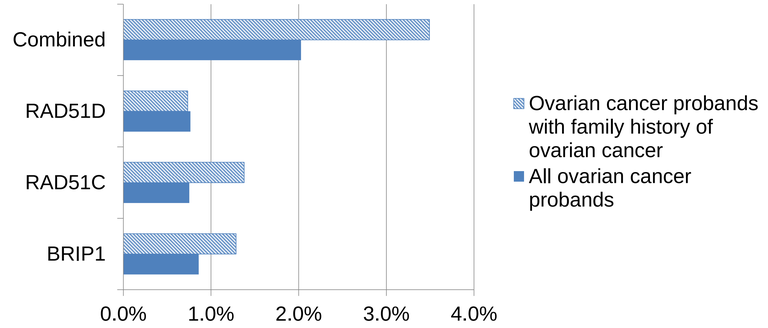
Table 1. Patient Demographics

Demographic	N	%
Panel Ordered	7449	
BreastNext	135	1.8%
OvaNext	5630	75.6%
CancerNext/CancerNext-Expanded	1684	22.6%
Ethnicity	7449	
African American/Black	283	3.8%
Ashkenazi Jewish	333	4.5%
Asian	367	4.9%
Caucasian	5334	71.6%
Hispanic	333	4.5%
Other/Unknown	799	10.7%
Median age at testing (range)	62	(17 – 90+)
Median age at ovarian cancer diagnosis (range)	57	(11 – 90+)
Additional primary cancer(s)	2071	27.8%

METHODS

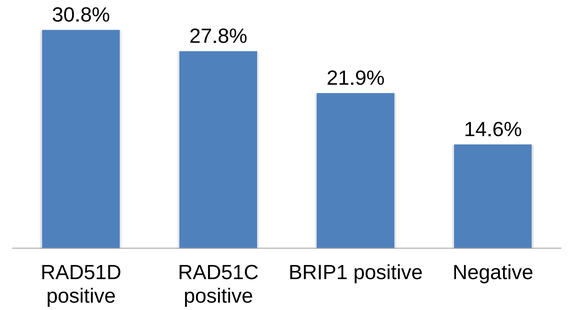
- All cases of ovarian (n=6739, 90.5%), primary peritoneal (n=356, 4.8%), or fallopian tube cancer (n=354, 4.8%) submitted for hereditary MGPT including sequencing and deletion/duplication analysis of *BRIP1*, *RAD51C*, and *RAD51D* between October 2013 and June 2016 were retrospectively reviewed.
- Clinical and family histories were obtained from test requisition forms and clinical documentation.
- Patients with borderline or non-epithelial pathologies (when known) were excluded from analysis.
- Test results of 101 family members of probands with a pathogenic mutation or likely pathogenic variant (VLP) in *BRIP1*, *RAD51C*, and *RAD51D* were reviewed.

Figure 1. Mutation Frequency



- Overall, 2.0% of patients with ovarian, primary peritoneal, or fallopian tube cancer were found to harbor a pathogenic mutation or VLP in *BRIP1* (n=64), *RAD51C* (n=56, or *RAD51D* (n=151).
- 3.5% (n=38) of 1088 probands with at least one first- or second-degree relative with ovarian cancer were found to harbor a pathogenic mutation or VLP in *BRIP1* (n=14), *RAD51C* (n=15), or *RAD51D* (n=8).
- 48 of 101 (47.5%) family members that underwent testing were found to harbor the familial pathogenic or VLP in *BRIP1*, *RAD51C*, or *RAD51D*.

Figure 2. Family History of Ovarian Cancer



TAKE-HOME POINTS

- Pathogenic mutations in *BRIP1*, *RAD51C*, and *RAD51D* (2.0%-3.5%) are frequent enough to warrant evaluation of these genes.
- The identification of mutations in ovarian cancer probands provides a key opportunity to identify at-risk family members appropriate for genetic testing and, if found to be mutation-positive, pursue risk-reducing salpingo-oophorectomy, as recommended by NCCN.

REFERENCES

1. National Comprehensive Cancer Network Guidelines Genetic/Familial High-Risk Assessment: Breast and Ovarian Version 2.2017
2. Ramus *et al.* Germline mutations in the *BRIP1, BARD1, PALB2,* and *NBN* genes in women with ovarian cancer. J Natl Cancer Inst. 2015. 107(11).
3. Song *et al.* Contribution of germline mutations in the *RAD51B, RAD51C,* and *RAD51D* genes to ovarian cancer in the population. J Clin Oncol. 2015. 33 (26): 2901-7.
4. Loveday C, *et al.* Germline *RAD51C* mutations confer susceptibility to ovarian cancer. Nat Genet. 2012;44(5):475-6; author reply 6.
5. Loveday C, *et al.* Germline mutations in *RAD51D* confer susceptibility to ovarian cancer. Nat Genet. 2011;43(9):879-82.

15 Argonaut, Aliso Viejo, CA 92656 Toll Free 866 262 7943 Fax 949 900 5501 ambrygen.com