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

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REFERENCES
2. Francis et al. Sensitivity mutations in the BRIP1, BRCA1, -2, and NBN genes in women with ovarian cancer. Proc Natl Acad Sci USA. 2011;108(26):10516-21

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) and family members that underwent testing were found to harbor the familial pathogenic variant (VLP) in BRIP1, RAD51C, and RAD51D were reviewed.

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.

Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>N</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Panel Ordered</td>
<td>741</td>
<td>1.8</td>
</tr>
<tr>
<td>BreastNext</td>
<td>135</td>
<td>1.8</td>
</tr>
<tr>
<td>OvaNext</td>
<td>563</td>
<td>7.6</td>
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<tr>
<td>CancerNext/CancerNext-Exp</td>
<td>1684</td>
<td>22.6</td>
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<tr>
<td>Ethnicity</td>
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<td>African American/Black</td>
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<td>Ashkenazi Jewish</td>
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<tr>
<td>Asian</td>
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<tr>
<td>Caucasian</td>
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<td>7.6</td>
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<td>Hispanic</td>
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<td>4.5</td>
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<tr>
<td>Other/Unknown</td>
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<td>10.7</td>
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<tr>
<td>Median age at testing</td>
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<tr>
<td>Median age at ovarian cancer diagnosis</td>
<td>57</td>
<td>(11 – 90+)</td>
</tr>
<tr>
<td>Additional primary cancer</td>
<td>2071</td>
<td>27.8</td>
</tr>
</tbody>
</table>

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=14), 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=15).
- 48 of 101 (47.5%) family members that underwent testing were found to harbor the familial pathogenic or VLP in BRIP1, RAD51C, or RAD51D.

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.

Figure 2. Family History of Ovarian Cancer

- 30.8% positive
- 27.8% positive
- 21.9% positive
- 14.6% negative

Figure 3. Frequency of Pathogenic Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes in a Population of 1,088 Probands with at Least One First- or Second-Degree Relative with Ovarian Cancer

- 2.0% positive
- 3.5% positive
- 47.5% positive
**Frequency of Germline Mutations in **BRIP1, **RAD51C, and **RAD51D **Among Women with Ovarian, Primary Peritoneal, and Fallopian Tube Cancer**

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Ambry Genetics

**Objectives:** 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. We aimed to determine the frequency of pathogenic germline mutations in these genes among women with ovarian cancer referred for hereditary cancer multigene panel testing.

**Methods:** All cases of ovarian (n=6739, 90.5%), primary peritoneal (n=356, 4.8%), or fallopian tube cancer (n=354, 4.8%) submitted to our laboratory for hereditary cancer panels including sequencing and deletion/duplication analysis of **BRIP1, **RAD51C, and **RAD51D between October 2013 and June 2016 were retrospectively reviewed. Clinical and family histories, as provided by clinicians on test requisition forms or via clinical documentation, and molecular results were reviewed. When pathology was provided (n=1866, 24.4%), patients with borderline or non-epithelial pathologies were excluded from analysis (n=185, 2.4%). Test results of 101 family members of probands with a pathogenic mutation or likely pathogenic variant in **BRIP1, **RAD51C, and **RAD51D were reviewed.

**Results:** Overall, 2.0% (151/7449) of patients with ovarian, primary peritoneal, or fallopian tube cancer were found to harbor a pathogenic mutation or likely pathogenic variant in **BRIP1 (n=64, 0.9%), **RAD51C (n=56, 0.8%), or **RAD51D (n=151, 2.0%). Among 1088 probands with at least one first- or second-degree relative with ovarian cancer, 3.5% (n=38) were found to harbor a pathogenic mutation in **BRIP1 (n=14, 1.3%), **RAD51C (n=15, 1.4%), or **RAD51D (n=8, 0.7%). Of the 101 family members that underwent testing, 48 (47.5%) were found to harbor the familial pathogenic or likely pathogenic variant in **BRIP1, **RAD51C, or **RAD51D.

**Conclusions:** Pathogenic mutations in **BRIP1, **RAD51C, and **RAD51D (2.0%-3.5%) are frequent enough to warrant evaluation of these genes. Furthermore, 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.