The Genetic Basis of Ovarian Cancer: Identifying Hereditary Ovarian Cancer Using a 25-gene Panel

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Presented at SGO Annual Meeting on Women's Cancer - March 2015
Background

- Mutations in hereditary cancer susceptibility genes account for up to 20% of all ovarian cancers.
- Identifying patients with hereditary cancer provides an opportunity to:
  - Prevent 2nd cancer
  - Notify family members regarding cancer risk
  - Enroll patients in clinical trials for new treatments
- All patients with epithelial ovarian cancer meet NCCN guidelines for BRCA1 and BRCA2 testing (Risch et al. AJHG 2001).
- Patients with ovarian cancer and personal or family history of colon and/or endometrial cancer may also meet guidelines for Lynch syndrome testing.
- With next-generation sequencing, patients receiving hereditary cancer testing can be tested for more genes using a multi-gene panel approach.

Methods

- We queried a commercial laboratory database for patients affected with ovarian cancer (including fallopian tube and peritoneal cancer).
- All patient data regarding clinical history was obtained by health care provider report on test requisition forms.
- Analysis included 3,088 patients (September 2013 - November 2014).
- Panel based on next generation sequencing and rearrangement analysis of 25 genes with cancer risk data: BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, EPCAM, APC, MUTYH, CDKN2A, CDK4, PALB2, CHEK2, SMAD4, BMPR1A, STK11, TP53, CDH1, PTEN, ATM, NBN, BARD1, BRIP1, RAD51C, and RAD51D.
- Panel limited to genes with strong evidence of cancer association.

Results

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th># of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary</td>
<td>2868 (92.9%)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>71 (2.3%)</td>
</tr>
<tr>
<td>Fallopian Tube</td>
<td>65 (2.1%)</td>
</tr>
<tr>
<td>Ovary (non-epithelial)</td>
<td>60 (1.9%)</td>
</tr>
<tr>
<td>Ovary and Fallopian Tube</td>
<td>16 (0.5%)</td>
</tr>
<tr>
<td>Ovary and Peritoneum</td>
<td>8 (0.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>3,088</td>
</tr>
</tbody>
</table>
Panel Test Results

- 13.6% (419/3,088) patients were identified as having a pathogenic or likely pathogenic mutation.
- 86.4% (2,669/3,088) patients were mutation negative.
- Seven patients had two mutations.

### Distribution of mutations in BRCA1/BRCA2 and Lynch syndrome genes*

- **BRCA1/BRCA2**: 65%
- Lynch syndrome: 7.8%
- Other: 27.2%

*426 mutations detected in 419 patients

### Distribution of mutations in ‘other’ genes*

- ATM: 20.62%
- BRIP1: 18.12%
- CHEK2: 16.42%
- PALB2: 11.21%
- RAD51C: 16.42%
- RAD51D: 3.4%
- BARD1: 3.4%
- APC: 1.7%
- TP53: 1.7%
- p16: 0.9%
- PTEN: 0.9%
- NBN: 5.2%

*ATM and BRIP1 were the most common other genes found to have a mutation

### Patients with two deleterious mutations

<table>
<thead>
<tr>
<th>Gene Pair</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1, ATM</td>
<td>2</td>
</tr>
<tr>
<td>BRCA1, BARD1</td>
<td>1</td>
</tr>
<tr>
<td>BRCA1, PMS2</td>
<td>1</td>
</tr>
<tr>
<td>BRCA2, ATM</td>
<td>1</td>
</tr>
<tr>
<td>BRCA2, p16</td>
<td>1</td>
</tr>
<tr>
<td>BRCA2, PALB2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7</strong></td>
</tr>
</tbody>
</table>

### Variants of uncertain significance in tested patients

- 63.1% NO VUS
- 27.9% 1 VUS
- 7.4% 2 VUS
- 1.3% 3 VUS
- 0.3% 4 VUS

### Conclusions

- 13.6% of patients had at least one pathogenic mutation identified with a 25-gene hereditary cancer panel.
  - 65.0% of mutations were in BRCA1 and BRCA2.
  - 7.8% of mutations were in the Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2).
  - 27.2% of mutations were in other hereditary cancer genes.
- ATM and BRIP1 were the most common other genes found to have a mutation.
- Panel testing led to a 53.8% increase in the identification of deleterious mutations over BRCA1 and BRCA2 testing alone.
- Panel testing in this series led to the identification of mutations in genes that would not otherwise be suspected by clinical or family history alone.