We reviewed the clinical features of patients tested for mutations in CDH1. Estimated cancer risks to age 80 are up to 80% for diffuse gastric cancer and 52% for female invasive lobular breast cancer. Current testing criteria for CDH1 require that a patient has at least some personal or family history of diffuse gastric cancer. We identified individuals with CDH1 pathogenic variants (PVs) (those classified as Deleterious or Suspected Deleterious) through clinical testing with a 25-gene hereditary cancer panel between September 2013 and June 2015. Individuals who underwent targeted analysis for CDH1 PVs previously identified in relatives were excluded. Clinical histories were obtained from test request forms submitted by healthcare providers at the time of testing.

**METHODS**

- We identified individuals with CDH1 pathogenic variants (PVs) (those classified as Deleterious or Suspected Deleterious) through clinical testing with a 25-gene hereditary cancer panel between September 2013 and June 2015.
- Individuals who underwent targeted analysis for CDH1 PVs previously identified in relatives were excluded.
- Clinical histories were obtained from test request forms submitted by healthcare providers at the time of testing.

**RESULTS**

- CDH1 pathogenic variants were identified in 47 apparently unrelated probands.
  - 44 Female and 3 Male
- Only 16/47 (34.0%) of these individuals reported a personal and/or family history of gastric cancer (Figure 1, Figure 2).
- 22/47 (46.8%) of individuals with a PV in CDH1 reported a personal history of breast cancer, with 7 specified as lobular invasive (Figure 1).

  **Table 1. Clinical Testing Criteria for CDH1**

<table>
<thead>
<tr>
<th>International Gastric Cancer Linkage Consortium³</th>
<th>National Comprehensive Cancer Network⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 GC cases regardless of age, at least one confirmed DGC&lt;40y</td>
<td>2 GC cases, one confirmed DGC &lt;50y</td>
</tr>
<tr>
<td>Personal or family history of DGC and LBC, one diagnosed &lt;50y</td>
<td>Personal or family history of DGC and LBC, one diagnosed &lt;50y</td>
</tr>
</tbody>
</table>

GC: gastric cancer; DGC: diffuse gastric cancer; LBC: lobular breast cancer

- 2/47 (4.3%) reported a personal history of colorectal cancer.
- 2 individuals were identified as having a second PV.
  - One in CHEK2 and one in BRCA1.
- All variants classified as pathogenic in this study are predicted to lead to loss of CDH1 function through premature truncation or disruption of a functional domain of the protein - no missense variants are classified as PVs (Table 2).

<table>
<thead>
<tr>
<th>Type of Variant</th>
<th>Number of Unique Variants</th>
<th>Number of Individuals (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single or Multi-exon deletion</td>
<td>4</td>
<td>6 (12.8%)</td>
</tr>
<tr>
<td>Nonsense / Frameshift</td>
<td>21</td>
<td>30 (63.8%)</td>
</tr>
<tr>
<td>Splice Site</td>
<td>8</td>
<td>11 (23.4%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>33</td>
<td>47</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

- This study demonstrates that PVs in CDH1 can be identified in individuals with no personal or family history of gastric cancer and who do not meet HDGC testing criteria.
- CDH1-positive individuals in this cohort are more likely to have a personal history of breast and/or gastric cancer, relative to the overall testing population for the 25-gene panel.
- The CDH1 PVs reported here represent clinically actionable results based on current professional society guidelines.
- These findings illustrate that a multi-gene panel can identify individuals at risk for HDGC who would have been missed with single syndrome testing or cancer-specific panels based on reported cancer history.

**REFERENCES**