Cancer Risks Associated with Germline Pathogenic Variants in the MLH1, MSH2, MSH6, PMS2, and EPCAM Genes

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Results

- LS PVs were detected in 0.9% (9,651/1,064,399) of the study population.
- The highest number of PVs were observed in PMS2 (N=3,587), followed by MSH6 (N=2,770), MSH2 (N=1,910), MLH1 (N=1,376) and EPCAM (N=34). PVs in EPCAM were too rare for evaluation of cancers other than colorectal cancer.
- Table 1 shows the prevalence of LS PVs among patients diagnosed with different cancers.
- PVs in all genes were significantly associated with colorectal cancer; ORs ranged from 14-fold for MLH1 to 2-fold for PMS2 (Figure 1).
- PVs in MLH1, MSH2, MSH6, and PMS2 were significantly associated with uterine cancer, with ORs ranging from 6-fold for MSH2 to 2-fold for PMS2 (Figure 1).
- MLH1 and MSH2 PV carriers had 4- and 2-fold increased risks of gastric cancer, respectively (Figure 1).
- PVs in MLH1, MSH2, and MSH6 were significantly associated with ovarian cancer, with ORs ranging from 4-fold for MSH2 and 2-fold for MLH1 and MSH6 (Figure 1).

Background

- Lynch syndrome (LS) is caused by germline pathogenic variants (PVs) in the mismatch repair genes (MLH1, MSH2, MSH6, PMS2) or the EPCAM gene.
- LS is associated with high risks of various cancers, notably colorectal and uterus; however, gene-specific estimates of risk have been limited, especially for the lower penetrance genes MSH6 and PMS2.

Methods

- We examined clinical and genetic records from a consecutive cohort of 1,064,399 patients referred for hereditary cancer testing between 9/2013 - 9/2023.
- We estimated the prevalence of LS PVs in the full cohort and within patients diagnosed with different cancers.
- Cancer associations of each LS gene were estimated as odds ratios (ORs), with 95% confidence intervals (CIs), from multivariable logistic regression models adjusted for personal and family cancer history, age, ancestry, and sex (where applicable).

Conclusions

- We confirmed a higher prevalence of PMS2 and MSH6 compared to MSH2 and MLH1 among LS PV carriers.
- Our data provide gene-specific cancer risks for PMS2 and MSH6 where current literature is limited.
- These results may inform gene-specific cancer risk counseling for LS PV carriers.

Table 1: Prevalence of Lynch Syndrome Genes

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Total Patients</th>
<th>MLH1 (Number)</th>
<th>MSH2 (Number)</th>
<th>MSH6 (Number)</th>
<th>PMS2 (Number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal*</td>
<td>25,408</td>
<td>590 (2.3%)</td>
<td>593 (2.3%)</td>
<td>407 (1.6%)</td>
<td>340 (1.3%)</td>
</tr>
<tr>
<td>Uterine</td>
<td>19,328</td>
<td>143 (0.7%)</td>
<td>301 (1.6%)</td>
<td>484 (2.5%)</td>
<td>225 (1.2%)</td>
</tr>
<tr>
<td>Gastric</td>
<td>1,059</td>
<td>17 (1.6%)</td>
<td>15 (1.4%)</td>
<td>4 (0.4%)</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>25,840</td>
<td>29 (0.1%)</td>
<td>301 (1.6%)</td>
<td>484 (2.5%)</td>
<td>225 (1.2%)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>5,747</td>
<td>3 (0.1%)</td>
<td>17 (0.3%)</td>
<td>16 (0.3%)</td>
<td>19 (0.3%)</td>
</tr>
<tr>
<td>Renal</td>
<td>2,383</td>
<td>8 (0.3%)</td>
<td>30 (1.3%)</td>
<td>10 (0.4%)</td>
<td>9 (0.4%)</td>
</tr>
<tr>
<td>Breast</td>
<td>173,945</td>
<td>69 (&lt;0.1%)</td>
<td>104 (0.1%)</td>
<td>275 (0.2%)</td>
<td>443 (0.3%)</td>
</tr>
<tr>
<td>Unaffected</td>
<td>720,506</td>
<td>557 (0.1%)</td>
<td>786 (0.1%)</td>
<td>1,440 (0.2%)</td>
<td>2,227 (0.3%)</td>
</tr>
</tbody>
</table>

*There were 13 individuals with colorectal cancer who had a PV in EPCAM.

Figure 1: Gene-Specific Cancer Risks Associated with Lynch Syndrome Genes