EXAMINING SEVERITY OF CANCER HISTORY IN PATIENTS WITH PATHOGENIC VARIANTS IN ATM

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BACKGROUND

• Germline pathogenic variants (PVs) in the ATM gene are known to cause the recessive condition Ataxia-Telangiectasia (A-T), a neurodegenerate disease.1
• Individuals with a single ATM PV are known to have an increased risk for female breast cancer and pancreatic cancer.2,3
• Published reports differ on the theory of a particular type of PV in ATM conferring a different level of cancer risk.4-6 We tested the hypothesis that different types of PVs confer different levels of cancer risk by comparing the cancer histories of individuals carrying different types of PVs.

METHODS

• Individuals ascertained for suspected hereditary cancer risk were tested with a clinical 25-gene hereditary cancer panel between September 20, 2013 and June 12, 2015.
• Clinical information for those with PVs in ATM was obtained via healthcare provider report on the test request forms.
• Variants with a laboratory classification of Deleterious or Suspected Deleterious were regarded as pathogenic.
• 33 individuals with PVs in ATM and another gene were excluded from the cohort.
• Missense variants in ATM were classified as pathogenic if they are known to contribute to the classic form of A-T. The missense PV c.7271T>G (p.Val2424Gly) may carry higher cancer risks than other PVs in ATM.7,8 For this reason, we examined this variant separately from other missense PVs.

RESULTS

In total, 657 individuals were found to carry a PV in ATM (Table 1).
• Approximately 25% of women with different types of PVs in ATM had a personal diagnosis of breast cancer at or before age 50 (Figure 1).
• 33 individuals (32 women, 1 man) were found to carry the variant c.7271T>G.
• 11/32 (34.4%) women with c.7271T>G had a personal diagnosis of early onset breast cancer.

Table 1. Pathogenic Variant Types in ATM

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frameshift/Nonsense</td>
<td>9</td>
<td>421</td>
</tr>
<tr>
<td>Splice</td>
<td>4</td>
<td>108</td>
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<tr>
<td>Missense</td>
<td>1</td>
<td>82</td>
</tr>
<tr>
<td>Large Rearrangement</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>642</td>
</tr>
<tr>
<td>Total Mutations</td>
<td>657</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Pathogenic Variant Types in ATM According to Personal and Family History

- 10/50 (20.0%) women with a different missense PV had a personal diagnosis of early onset breast cancer.
- Between 35% and 50% of all individuals with different types of PVs had a high-risk family history (Figure 1).
  - High-risk family history was defined as 3 or more diagnoses of breast and/or pancreatic cancer in the family, including the patient where applicable.

CONCLUSIONS

• This study identified no significant difference in cancer risks associated globally with different types of PVs.
• It appears that there is no evidence that variants in ATM present unique challenges for classification, although we cannot rule out higher or lower penetrance associated with individual variants.
• Women with the missense PV c.7271T>G were more likely to have a personal diagnosis of breast cancer ≤ 50 compared to women with other missense PVs, although this difference was not statistically significant.
• As additional families are identified, these findings can be confirmed and the relative cancer risks associated with individual ATM variants can be further characterized.

REFERENCES