Incidental MITF, p.E318K Pathogenic Variant in Three Independent Cases Undergoing Hereditary Cancer Risk Assessment

Jessica Ordonez
Miami Cancer Institute, jessicaord@baptisthealth.net

Jeffrey Boyd
Miami Cancer Institute, JeffreyB@baptisthealth.net

Arelis Martir-Negron
Baptist Health Medical Group; Miami Cancer Institute, arelisma@baptisthealth.net

Follow this and additional works at: https://scholarlycommons.baptisthealth.net/se-all-publications

Citation

This Conference Lecture -- Open Access is brought to you for free and open access by Scholarly Commons @ Baptist Health South Florida. It has been accepted for inclusion in All Publications by an authorized administrator of Scholarly Commons @ Baptist Health South Florida. For more information, please contact Carrief@baptisthealth.net.
**Incidental MITF, p.E318K Pathogenic Variant in Three Independent Cases Undergoing Hereditary Cancer Risk Assessment**

Jessica Ordonez, MS, CGC,1 Cristina Flanagan, MMSc, CGC,1,2 Jeff Boyd, PhD,1 & Arelis Martir-Negron, MD, FACMG,1

1 Miami Cancer Institute, Center for Genomic Medicine, Baptist Health South Florida; 2 Myriad Genetics Laboratory

---

**Background**

- The **MITF**, p.E318K mutation has been described as a rare risk factor for melanoma and renal cell carcinoma.
- Associated risks for the **MITF**, p.E318K mutation have been mostly ascertained by studying melanoma cohorts.
- Little is known about the incidence of **MITF**, p.E318K or the natural history of **MITF**, p.E318K carriers in non-melanoma cohorts.
- We describe three cases where the **MITF**, p.E318K mutation was incidentally identified during hereditary cancer risk assessment.

**Clinical History**

<table>
<thead>
<tr>
<th>Clinical History</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49</td>
<td>43</td>
<td>52</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Ethnicity/Race</td>
<td>Hispanic</td>
<td>Hispanic</td>
<td>Hispanic</td>
</tr>
</tbody>
</table>

- Personal history of cancer: Yes
- Location and pathology: Tumor in the head and neck, lung and breast.
- Reason for referral: Family history of breast, ovarian, and pancreatic cancer.
- Met HBOC genetic testing NCCN guidelines at assessment? Yes, Yes, No
- Met Lynch Syndrome genetic testing NCCN guidelines at assessment? No, No, Yes

**Family History**

**Genetic Test Results**

<table>
<thead>
<tr>
<th>Genetic Test Results</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variants of Unknown Significance</td>
<td><strong>FLCN</strong>, c.1579C&gt;T</td>
<td><strong>ATM</strong>, c.6820G&gt;A</td>
<td><strong>RAD51C</strong>, c.719T&gt;C</td>
</tr>
<tr>
<td>BRCA2, c.9925GA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MITF Risks & Proposed Recommendations**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Lifetime Risks</th>
<th>Screening</th>
<th>Age to begin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>~5-20% (vs. ~2.5% USA population risk)</td>
<td>Annual full body dermatologic exam</td>
<td>~20 y (Median age of onset 32-71 y)</td>
</tr>
<tr>
<td>Renal Cell Carcinoma (RCC)</td>
<td>~8% (vs. 1.6% USA population risk)</td>
<td>Consideration of annual renal imaging with renal ultrasound. Consider alternating with MRI.</td>
<td>~25-30 y (Median age of onset 35-72 y)</td>
</tr>
</tbody>
</table>

**Discussion**

- As multigene panel testing continues to gain popularity in clinical practice, incidential pathogenic variants are also more commonly identified.
- The challenge of incidental findings is heightened in genes with limited data on lifetime risks and incomplete penetrance.
- We highlight the importance of the development of clinical guidelines for newly described hereditary cancer genes to standardize recommendations, better understand risks for carriers in other populations, and justify medical necessity for management changes based on incidental genetic test results.
- Limitations:
  - Small sample size. Limited data on longitudinal follow-up to assess the clinical impact of incidental findings.

**References**


**Acknowledgements**

- We would like to thank our patients for their engagement in genetic risk assessment. We would also like to thank our entire team at the Division of Clinical Genetics for their tireless support!