BAP1 germline mutations
A new Cutaneous Nevus Melanoma Syndrome

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Listed as co-inventor

**US patent application US 61/463,389**

*BAP1* mutational analysis in determining susceptibility to melanocytic neoplasia and in the diagnosis, prognosis, and treatment of melanocytic neoplasia
Familial atypical mole - malignant melanoma syndrome
Familial atypical mole - malignant melanoma syndrome

- Characterized by hundreds of flat and brown nevi
- Patients should be monitored closely
- Patient’s melanoma-risk: up to 20%
- Some patients have germline mutations in CDKN2A
A new Cancer Predisposition Syndrome caused by *BAP1* Mutations

3 families with germline mutations in the *BAP1* gene:

**Family 1**

- Multiple epithelioid, melanocytic tumors
- Melanocytic tumor of uncertain malignant potential
- Cutaneous melanoma

**Family 2**

- Uveal melanoma
- Mesothelioma

**Family 3**

- BAP1 germline mutation
- BAP1 wildtype

*BAP1* gene structure:

- Family 1: c.1305delG
- Family 2: c.2057-2 A>G
- Family 3: c.79delG
Very subtle, clinical phenotype in patients with BAP1 germline mutations
Skin-lesions: Inconspicuous, skin-colored, dome-shaped papules
3 Families with germline mutations in the BAP1 gene

Family 2
Number of skin lesions varies from only a few to > 50
Resemble histologically ‘Atypical Spitz tumors’ (large, epithelioid cells)
Histological appearance of a representative lesion
Epithelioid phenotype is associated with loss of BAP1 expression

The epithelioid morphology and BAP1 immunohistochemistry enables the accurate identification of these tumors.
Epithelioid, melanocytic tumors may progress to melanoma

Despite the benign clinical appearance, epithelioid skin tumors should be observed and — if changing — excised.
Tumor Spectrum in Patients with BAP1 germline mutations

19 germline mutation carriers in 3 families

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>%</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelioid, melanocytic tumors</td>
<td>84.3</td>
<td>16/19</td>
</tr>
<tr>
<td>MELTUMPs</td>
<td>21.1</td>
<td>5/19</td>
</tr>
<tr>
<td>Cutaneous melanoma</td>
<td>26.3</td>
<td>4/19</td>
</tr>
<tr>
<td>Pleural mesothelioma</td>
<td>15.8</td>
<td>3/19</td>
</tr>
<tr>
<td>Peritoneal mesothelioma</td>
<td>15.8</td>
<td>3/19</td>
</tr>
<tr>
<td>Uveal melanoma</td>
<td>10.5</td>
<td>2/19</td>
</tr>
</tbody>
</table>

Other investigators suggested also a predisposition to
- **Lung adenocarcinoma** (Abdel-Rahman et al. 2011)
- **Meningioma** (Abdel-Rahman et al. 2011)
- **Clear cell renal cell carcinoma** (Pena-Llopis et al. 2012)
- **Paraganglioma** (Wadt et al. 2013)
When should we test patients for BAP1 germline mutations?

**ASCO recommends genetic testing only under 3 conditions:**

1. Individual being tested has a personal or family history suggestive of genetic cancer susceptibility.
   - **Melanocytic tumors:** epitheloid nevi (ASTs), melanocytic skin tumor of uncertain malignant potential, cutaneous melanoma, uveal melanoma
   - **Mesothelioma**
   - **Other cancers:** lung adenocarcinoma, meningioma, clear cell renal cell carcinoma, paraganglioma, bladder cancer, breast cancer...

2. The genetic test can be adequately interpreted

3. Test results aid in diagnosis or influence the medical or surgical management of the patient or family members.


Robson *et al.* J Clin Oncol (2010)
Influence of *BAP1* germline mutation on the medical or surgical management

**Cutaneous, melanocytic tumors:**
- Regular dermatologic examination
- Establish the presence/absence of epithelioid, melanocytic tumors
- If present, monitor for any changes
- Removal of changing lesions (they may progress to cutaneous melanomas)
- Exposure to UV-radiation may increase risk: extensive sun-protection

**Eyes:**
- Regular examinations by an ophthalmologist

**Mesotheliomas:**
- Regular examinations and monitoring with biomarkers e.g. Fibulin-3?
- Check and avoid exposure to asbestos and erionite

**Other Cancer:**
- Regular check-ups to detect malignancies early?
Currently, we do not know:

- Relative risk of patients to develop cancer?
  Is \( BAP1 \) a low-, intermediate-, and high penetrance gene for cancer?
- What is the full tumor spectrum of \( BAP1 \) germline mutation carriers?
- Frequency of \( BAP1 \) mutation in the general population?
Germline vs. somatically acquired BAP1 mutations

**Germline mutations**
- Mutations are present in all cells (including egg and sperm)
- Can be inherited
- Cause cancer predisposition syndromes
- Only one more hit is necessary in somatic cells

- **Normal cell**
  - 1st hit present in all cells

- **Cancer cell**
  - 2nd hit – only 1 somatic hit necessary

- Inheritable
- Progeny has increased risk

**Somatic mutations**
- Mutations occur only in non-germline tissue (e.g. melanocytes, renal cells)
- Can cause cancer
- Cannot be inherited
- Two hits are necessary in somatic cells

- **Normal cell**
  - 2 normal alleles – no mutations

- **Cancer cell**
  - 2 hits necessary – low probability

- Non-inheritable
- Progeny has normal risk
Sporadic ‘Atypical Spitz Tumor’ with somatically acquired \textit{BAP1} loss
Large epithelioid and pleomorphic melanocytes; loss of BAP1 expression

BAP1: c.459del, p.E154Rfs*33

BRAF: c.1799T>A, p.V600E
Loss of BAP1 marks the transition from a nevus to a melanoma

Sporadic melanoma arising in a nevus
60-year-old patient, back
Nevus part: small nevoid cells, $BRAF^{V600E}$ mutation, no $BAP1$ loss
Melanoma part: highly atypical cells, $BRAF^{V600E}$ mutation, $BAP1$ loss
Proliferation stain (Ki-67): High cell mitotic index in the melanoma part
## Somatic BAP1 mutations in Cancer

<table>
<thead>
<tr>
<th>Primary tissue</th>
<th>% Mutated</th>
<th>Mutated samples</th>
<th>Total samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uveal Melanoma</td>
<td>43.1</td>
<td>41</td>
<td>95</td>
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<tr>
<td>Mesothelioma</td>
<td>26.9</td>
<td>51</td>
<td>189</td>
</tr>
<tr>
<td>Clear Cell Renal Cell Carcinoma</td>
<td>13.0</td>
<td>58</td>
<td>446</td>
</tr>
<tr>
<td>Bladder Cancer</td>
<td>5.4</td>
<td>2</td>
<td>37</td>
</tr>
<tr>
<td>Cutaneous Melanoma/AST</td>
<td>3.5</td>
<td>13</td>
<td>363</td>
</tr>
<tr>
<td>Endometrium Carcinoma</td>
<td>1.4</td>
<td>3</td>
<td>204</td>
</tr>
<tr>
<td>Lung Carcinoma</td>
<td>1.1</td>
<td>11</td>
<td>929</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>1.0</td>
<td>4</td>
<td>376</td>
</tr>
<tr>
<td>Ovary Carcinoma</td>
<td>0.6</td>
<td>4</td>
<td>665</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>0.5</td>
<td>4</td>
<td>691</td>
</tr>
<tr>
<td>Colon Carcinoma</td>
<td>0.4</td>
<td>3</td>
<td>689</td>
</tr>
</tbody>
</table>
## Summary - Loss of BAP1

### Germline BAP1 mutations

- Epithelioid melanocytic tumors – Atypical Spitz tumors ("ASTs")
- Uveal melanoma
- Cutaneous melanoma
- Mesothelioma
- (and possible other tumors like renal cell carcinoma, paraganglioma)

### Sporadic BAP1 mutations

- "AST" - characterized by BRAF mutation and loss of BAP1 (BAP1oma)
- Uveal melanoma (40%)
- Cutaneous melanoma (5%)
- Mesothelioma (25%)
- Clear cell renal cell cancer (10%)

Patients with a personal or family history of these tumors should be tested for BAP1 mutations.