**Hereditary Melanoma**

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### Definition of Hereditary Melanoma

- A family with two or more first degree relatives with malignant melanoma
- In Australia or the US requires three or more relatives with melanoma
- An individual with three or more melanomas regardless of family history
- Melanoma or pancreatic cancer in three or more family members

### Clinical Features of Hereditary Melanoma

- Earlier age at onset
- Multiple primaries
- Geographic location of the individual is important. Regions of the world with more sun, i.e. Australia and the US mutation carriers get more melanomas
- Penetrance is variable: In the US 50% of mutation carriers get melanoma by age 50, and 76% by age 80

### Table 1. Clinical Features of Hereditary and Sporadic Melanoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hereditary Melanoma</th>
<th>Sporadic Melanoma</th>
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</thead>
<tbody>
<tr>
<td>Median Age (yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36</td>
<td>57</td>
</tr>
<tr>
<td>Female</td>
<td>29</td>
<td>50</td>
</tr>
<tr>
<td>Diagnosis before age 20</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Multiple primary melanomas</td>
<td>30%</td>
<td>4%</td>
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<tr>
<td>Melanoma subtype (predominant)</td>
<td>SSM</td>
<td>SSM</td>
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<tr>
<td>Presence of dysplastic nevi</td>
<td>Majority</td>
<td>~ 10%</td>
</tr>
<tr>
<td>Positive family history of melanoma</td>
<td>100%</td>
<td>~</td>
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<td>SSM = superficial spreading melanoma</td>
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</tbody>
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Greene, M; Cancer 86, 1999

### Mode of Inheritance

Prevalence of Hereditary Melanoma

- Sporadic melanoma
- CDK4/2A
- Unknown genes
- CDK6 and PI4ARF

**Proportion of Gene Mutations**
CDKN2A is a tumor suppressor gene. This gene codes for the p-16 protein which suppresses the Oncogene CDK4. CDK4 stimulates cell growth by acting on Rb protein. Some subgroups of the CDKN2A gene mutation have a 17% risk of pancreatic cancer. Avg. risk is 1.3%.

CDK4 makes up less than 1% of hereditary melanoma. It is an Oncogene. When it is mutated it is resistant to the suppressor effect of p-16 protein.

Screening Recommendations
- First skin exam before age 10
- Skin exam every 6 to 12 months
- Low threshold for excisional biopsy
- Clinical photographs or Mole Mapping is recommended to better identify changes in moles
- Photoprotection: decrease sun exposure and use of sun screens

When Should Genetic Testing Be Performed
- When there is a reliable test available to detect mutation carriers
- When carriers have a much higher risk of disease than non-carriers
- When there are good prevention strategies available to reduce cancer risk
- When early detection improves survival

What About Hereditary Melanoma?
- The Jury Is Out
  - Melanoma Genetics Consortium: Testing is not appropriate for routine use. JCO 1999; 17:3245-3251
  - Enrollment in research protocols is encouraged, but clinical genetic testing for melanoma is appropriate for selected patients (Hansen et al., The Lancet Oncology 5, 314-319, 2004)
Why Is There Controversy About Testing?

- Family members who test negative for gene mutation do not carry the same risk of malignant melanoma as the average population.
- Despite finding melanomas earlier in the monitored high risk families, there has not been a decline in melanoma mortality documented
- How do you screen for pancreatic cancer?

Pancreatic Cancer Screening

- Clinical Trials: Periodic Endoscopic Ultrasound
- MRI surveillance

Conclusions

- Hereditary Melanoma makes up between 6-10% of all Melanoma
- The majority of the genes associated with Hereditary Melanoma are still unknown
- Prevention modalities include early and frequent screening, photographs of lesions for accurate surveillance, low threshold for excisional biopsy, protection from the sun

Conclusions

- Early detection has not be shown to improve survival.
- Enrollment of patients in clinical trials is encouraged