The incidence of malignant melanoma has increased significantly over the past two decades in the white populations of various industrialised countries, making the disease more prominent. Melanoma accounts for approximately 4 and 5% of all new malignancies in males and females respectively. Melanoma may develop within a pre-existing benign melanocytic naevus, complicate a dysplastic naevus, arise de-novo, or rarely, evolve within a cellular blue naevus or other dermal dendrocytosis.

Subtypes of Cutaneous Melanoma

There are four main recognised subtypes of cutaneous melanoma, all of which display their own unique molecular alterations.

Superficial Spreading Melanoma

Superficial spreading melanoma is the most common variant and shows an equal sex incidence. The most common sites of involvement are the leg and back. The lesion usually presents as a flat scaly macule or plaque, which after a variable period of time develops a blue or black nodule of invasive melanoma (Figures 1–3).

Acral Lentiginous Melanoma

Acral lentiginous melanoma accounts for 8–10% of melanomas in Caucasians, but is the predominant subtype affecting Afro-Caribbeans and Asians. It is usually found on the digits (especially beneath the nails) and weight bearing areas, and usually presents as an irregular, gradually enlarging and variably pigmented macule.

Nodular Melanoma

Nodular melanoma accounts for 3–4% of all melanoma and has no radial growth phase and a poor prognosis. It affects males more than females (2:1) and generally arises in the 5th and 6th decade.

Lentigo Maligna and Lentigo Maligna Melanoma

Lentigo maligna and lentigo maligna melanoma typically develops in chronic sun-damaged skin of the elderly. Sites of predilection are the malar region, nose, temple and forehead. It usually presents as a variably pigmented, gradually enlarging, irregular flat macule. The in-situ lesion is often present for 10–15 years before invasive tumour develops.

Mutations

Melanoma has long been recognised for its general resistance to systemic therapy, with devastating outcomes for patients in the face of distant metastases. The relatively recent molecular epidemiology and classification of melanoma has lead to the realisation that this malignancy can be treated using specific agents for the molecular derangements that are prelevant in different melanoma subtypes.

**KIT Mutations**

Activating mutations in *KIT* are primarily found in the mucosal and acral lentiginous subtypes of melanoma. *KIT* mutations are seen in 20% of cases and shows point mutations in exons 11,13 and 17 with exon 11 being the most common. Demonstration of a *KIT* mutation in melanoma is associated with response to agents that inhibit *KIT* such as imatinib mesylate.

**BRAF Mutations**

Mutations in *BRAF* occur primarily in melanomas on intermittently sun damaged skin (approximately 50% of cases). *BRAF* mutations are noted in a roughly equal proportion of acquired naevi and appear to drive these lesions to senescence.

A melanoma mutated *BRAF* represent a therapeutic target that can be inhibited by a class of drugs that are active against the V600E *BRAF* mutation and probably a few of the other common variants of *BRAF* mutation including V600K that constitute the majority of mutated cases.

**NRAS Mutations**

NRAS mutations occur at a prevalence of 10–15% across multiple melanoma subtypes including cutaneous, acral and mucosal forms. There is not currently a solid clinical use for NRAS genotyping. Most mutation occur at exon 3 codon 61. NRAS status may suggest a somewhat likelihood of responding to IL-2 immunotherapy and patients with NRAS mutations may have a worse outcome than those with *BRAF* mutations treated with an inhibitor or those lacking mutations in both of these genes.

Clinical trials are currently underway to test which inhibitors may be most effective against melanomas harbouring NRAS mutations. Because KIT, NRAS and BRAF lie serially in a common signalling pathway, mutations in their coding genes are mutually exclusive.
Melanoma Subtypes

<table>
<thead>
<tr>
<th></th>
<th>Cutaneous</th>
<th>Acral</th>
<th>Mucosal</th>
<th>Uveal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td>Most common subtype</td>
<td>Involving skin on palms or soles</td>
<td>Mucosal surfaces of head and neck, gastrointestinal, or genitourinary tract</td>
<td>Arise from melanocytes in the ciliary tract of the eye</td>
</tr>
<tr>
<td><strong>Regions of Chromosome Gain</strong></td>
<td>6p, 7, 8q, 17q, 20q</td>
<td>6p, 7, 8q, 17q, 20q (Amp: 5p15, 5p13, 11q13, 12q14)</td>
<td>1q, 6p, 7, 8q, 11q13, 17q, 20q (Amp: 1q31, 4q12, 12q14)</td>
<td>6p, 8q</td>
</tr>
<tr>
<td><strong>Regions of Chromosome Loss</strong></td>
<td>9p, 10, 21q</td>
<td>6q, 9p, 10, 11q, 21q</td>
<td>3q, 4q, 6q, 8p, 9p, 10, 11p, 11q</td>
<td>3 (monosomy), 8p</td>
</tr>
<tr>
<td><strong>BRAF mutations</strong></td>
<td>50%</td>
<td>15%</td>
<td>5%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>NRAS mutations</strong></td>
<td>20%</td>
<td>10%</td>
<td>10%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>KIT mutations</strong></td>
<td>&lt;2% in Non-CSD (CSD: 2 – 17%)</td>
<td>15%</td>
<td>20%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>KIT amplifications</strong></td>
<td>0 – 7% in Non-CSD (CSD: 6%)</td>
<td>25%</td>
<td>25%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>GNAQ mutations</strong></td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>45%</td>
</tr>
</tbody>
</table>

CSD, chronic sun-damaged

**References:**

1. Weedon, Skin Pathology, 3rd Edition, Churchill Livingstone

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**Histopathology/Cytopathology**

Dr Fahey completed her Bachelor of Medicine and Bachelor of Surgery in 1998 at Monash University Medical School. During her time at Monash, she also completed a Bachelor of Medical Science - Forensic Pathology.

She is a Fellow of the Royal Australasian College of Pathologists and has held appointments at a number of hospitals. Dr Fahey was a Registrar in Anatomical Pathology at the Royal Women’s and Royal Children's Hospitals in 2004 and at the Royal Melbourne Hospital for four years from 2000 – 2003 and again in 2005.

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