MELANOMA AND INHERITED PREDISPOSITION

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Important points

- The most important factors that can influence an individual’s chance of developing melanoma are:
  - Sun exposure
  - The number of moles an individual has
  - The colour of an individual’s skin. A person who is fair-skinned is much more susceptible to skin damage and melanoma from sun exposure than someone with darker skin
  - Having a family history of melanoma
- A family history of melanoma can occur either just by chance, because cancer is common; because family members are exposed to the same environmental factors; or rarely (in 1%-2% of all cases), because a predisposition to melanoma is running in the family
- Inherited predisposition to melanoma is due to inheriting from either parent a faulty copy of just one of the genes that usually prevents melanoma from developing (a faulty ‘cancer protection’ gene)
  These genes are called CDKN2A and CDK4 respectively and we usually have working copies of these genes in our cells. An individual (male or female) who has a faulty CDKN2A or CDK4 gene copy and a individual copy of these genes is a carrier of a faulty melanoma gene and is predisposed to melanoma
  - The chance of developing melanoma is higher than in the average person if they inherit a faulty CDKN2A or CDK4 gene copy but, unless further changes occur over time in both copies of a number of additional other ‘cancer protection’ genes in skin cells, those cells will never become cancerous. The individual will not develop melanoma
- There is 1 chance in 2 (or 50%) in every pregnancy that a parent who is a carrier of a CDKN2A or CDK4 faulty gene will pass the faulty gene on to their child
- Guidelines have been developed for doctors to identify from their family history those at potentially high risk for melanoma and some other cancers due to inherited predisposition
  - For these families, genetic counselling is available to clarify an individual’s risk and discuss their options for genetic testing, its limitations, advantages and disadvantages and available prevention and early detection strategies
- Genetic testing for mutations in the CDKN2A and CDK4 genes is complex and involves
  - First, identifying the mutation in a family member who has or had melanoma (mutation search). This may take considerable time. At present this testing is restricted to research studies
  - Second, and only if a mutation is found, testing other family members without cancer to determine if they have inherited the faulty gene (predictive genetic testing).

In a small number of families in the community, there is an inherited predisposition to cancer. The cancers include

- Breast and ovarian cancer (see Genetics Fact Sheet 48)
- Bowel cancer (see Genetics Fact Sheet 49)
- Prostate cancer (see Genetics Fact Sheet 51) This Fact Sheet discusses inherited predisposition (susceptibility) to melanoma.

What is melanoma?

Melanoma is a type of skin cancer which:

- Is one of the most common cancers in young adults
- Usually occurs when some of the cells in a mole become cancerous
- Can occur anywhere on the skin (cutaneous melanoma) – even areas that do not get exposed to the sun
  - In men, it is often found on the trunk (the area from the shoulders to the hips) or the head and neck
  - In women, melanoma often develops on the lower legs
- In Australia, melanoma affects over their lifetime
  - 1 in 22 men
  - 1 in 33 women

The chance of developing melanoma increases with age, but it affects people of all age groups. Melanoma is one of the most common forms of cancer in young adults.

The structure of our skin

The skin has two main layers:

- The inner layer called the dermis
- The outer layer called the epidermis made up of three different types of cells:
  - Flat cells called squamous cells
  - Round cells called basal cells
  - Melanocytes which produce melanin, the pigment that gives our skin its natural colour. When skin is exposed to the sun, melanocytes produce more pigment, causing the skin to tan, or darken

Moles

Sometimes, clusters of melanocytes and surrounding tissue form benign (non-cancerous) growths called moles. Doctors also call a mole a naevus; the plural is naevi. They are very common and most people have between 10 and 40.

When moles are surgically removed, they normally do not return. Moles have a number of different characteristics. They

- Are flesh-coloured, pink, tan, or brown areas on the skin
- Can be flat or raised
- Are usually round or oval and vary in size
- May be present at birth or may appear later on — usually before age 40
- Generally have very small changes in size and character over a long period of time
- Tend to fade away in older people.

Often, but not always, melanoma occurs when the melanocytes in a mole become cancerous.
What causes melanoma?

There is no single cause. There are a number of factors (risk factors) which can influence an individual’s chance of getting melanoma. The most important are:

- Sun exposure
- The number of moles a person has
- The colour of an individual’s skin. A person who is fair-skinned is much more susceptible to skin damage and melanoma from sun exposure than someone with darker skin
- Having a family history of melanoma

What is meant by a family history of melanoma?

A family history of melanoma can occur:

- Just by chance, because cancer is common
- Because family members are exposed to the same environmental factors; for melanoma these include high sun exposure or having the same skin colouring
- Because a predisposition to melanoma is running in the family, though this is rare

A family history of melanoma means having one or more close blood relatives who have, or had, melanoma. These relatives could be on either the father’s or the mother’s side of the family. Close blood relatives (not relatives by marriage) are:

- Parents, siblings or children (first-degree relatives – 1°)
- Aunts, uncles, nephews, nieces or grandparents (second-degree relatives – 2°)

Many people may have a few relatives who have or had melanoma just because melanoma is common in Australia.

- Such people may be only slightly above the average risk
- Some people have a ‘stronger’ family history where a number of their close blood relatives have been affected with melanoma.
- Most of these people may have a moderately increased chance of developing melanoma
- A few will have a potentially high chance of developing melanoma because a predisposition to this cancer is running in their family

The more relatives an individual has who have or had melanoma, the higher their risk is for developing melanoma.

Inherited predisposition to the development of melanoma

The majority of melanoma cases are not due to an inherited predisposition to develop the condition.

A very small number (estimated at less than 1%-2%) of the cases of melanoma in Australia involve inherited predisposition to develop the cancer. In these cases, the individuals have inherited a copy of a faulty melanoma ‘cancer protection’ gene (see Genetics Fact Sheet 47 for further information about ‘cancer protection’ genes and inherited predisposition to cancer generally).

Cancer is a result of uncontrolled cell division and growth in cells in a particular part of the body, eg. in the cells of the skin: if the cells divide and grow out of control, they accumulate into a skin cancer.

We all have two copies of a number of different genes that normally control orderly growth and division of our cells throughout life. These genes can therefore be thought of normally acting as ‘cancer protection’ genes.

- All cancers can be considered genetic in origin because they arise from changes in the normal ‘cancer protection’ genes that we all have

A change (mutation) in the information in a ‘cancer protection’ gene makes the gene faulty and stops it doing its usual job in the skin cells. The cause of the changes that make the ‘cancer protection’ gene faulty is unknown, but may be due to a combination of genetic factors, environmental factors, and the process of ageing. The environmental factors may include exposure to various toxins, radiation, lifestyle and diet. Further research is being undertaken to more fully understand the cause of specific genetic mutations in the melanoma cells.

The development of melanoma is not a quick or simple process. It is a process involving a build-up of changes in a number of different ‘cancer protection’ genes in the cells of the skin over an individual’s lifetime (see Genetics Fact Sheet 47). This is why the development of melanoma can take many, many years, and is often seen in older people.

Most people are born having two working copies of each of the different ‘cancer protection’ genes in their cells. So that means that most people have not inherited a genetic predisposition to developing cancer and have an average chance of developing these cancers.

Between 1% and 2% of all melanomas are believed to be due to having inherited a faulty copy of one of the ‘cancer protection’ genes that usually control cell division and growth in cells called melanocytes in the skin (see Figure 50.1)

- From birth, the division and growth of cells in these individual’s skin tissue is not as tightly controlled as in other people in the population
- Although these cells would be on the first step on the staircase towards becoming cancerous, the other copy of that ‘cancer protection’ gene, and additional ‘cancer protection’ genes in the cells, are still working properly so the process of cell division and growth in the skin tissue are still largely normal. See Figures 47.2 and 47.3 in Genetics Fact Sheet 47 for more information about the progression to cancer
- The chance of developing melanoma is higher than average but unless further mutations occur over time in a number of other ‘cancer protection’ genes in skin cells, those cells will never become cancerous
- It is thought that not just one but many gene changes are needed for a melanoma to develop

It is important to remember that melanoma itself is not inherited, although cancer that arises from an inherited faulty ‘cancer protection’ gene is sometimes called hereditary cancer.
Two factors influence the pattern of inheritance of the faulty genes causing predisposition to melanoma, and where mutations in these genes are present in the affected individual's cells and the role of these genes is 'cancer protection'.

All men and women have two copies of the CDKN2A and CDK4 genes in their cells and the role of these genes is 'cancer protection'.

Unfortunately, the environmental factors that cause mutations to arise in the CDKN2A or CDK4 genes cannot be found. It is likely that there are a number of yet unidentified genes in which mutations predispose to melanoma. Research is continuing to try to identify these genes and their function. Genetic testing may not identify all possible gene changes.

What are the clues in a family history of melanoma that suggest that family members are at potentially high risk due to an inherited predisposition?

Documenting the health history of family members over several generations is important in determining if there is a faulty gene predisposing to developing melanoma. It is important to note:

- How the individual is related to you
- The type of cancer they have or had
- The age of the individual at the time of diagnosis

The family relationship is classified as:

- **First-degree relatives** (1°): parents, siblings or children
- **Second-degree relatives** (2°): aunts, uncles, nephews, nieces or grandparents

### What are the clues in a family history of melanoma?

- The age of the individual at the time of diagnosis
- The type of cancer they have or had
- The individual's lifetime of sun exposure, where an individual has a number of moles, and if they are fair-skinned

### What is the pattern of inheritance in families with a faulty CDKN2A or CDK4 gene?

Two factors influence the pattern of inheritance of the faulty CDKN2A or CDK4 genes in families:

#### 1. The CDKN2A and CDK4 genes are located on chromosomes 9 and 12 respectively. Both of these chromosomes are autosomes (one of the numbered chromosomes)

#### 2. The effects of changes in the CDKN2A or CDK4 genes are 'dominant' over the information in the working copy of the CDKN2A and CDK4 genes on the partner chromosomes 9 and 12 (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance in families of the faulty genes causing predisposition to melanoma is therefore described as **autosomal dominant inheritance** (see Genetics Fact Sheet 9). In Figure 50.2 the autosomal dominant faulty gene causing predisposition to melanoma is represented by 'D'; the working copy by 'd'.

Where one of the parents has or had melanoma involving a faulty CDKN2A or CDK4 gene or is a carrier of a faulty CDKN2A or CDK4 gene, **in every pregnancy**, each of their children has:

- 1 chance in 2 (50% chance) of inheriting the faulty gene from the affected parent
- 1 chance in 2 (50% chance) of **not** inheriting the faulty gene and only inheriting a working copy of the gene form both parents

Some important things to note:

- Melanoma will not develop in an individual who is a carrier of a faulty CDKN2A or CDK4 gene unless further mutations occur in additional other 'cancer protection' genes in the cells during their lifetime
- Children who have not inherited the faulty gene may still be at some increased risk of melanoma but cannot pass the faulty gene on to their own children
- While Figure 50.2 shows the father as the parent carrying the faulty CDKN2A or CDK4 gene, the same situation would arise if it was the mother

- A faulty CDKN2A or CDK4 gene can be inherited from either the mother or the father

- The environmental factors that cause mutations to arise in the CDKN2A or CDK4 gene(s) are still largely unknown. The identification of these factors and preventing their action paves the way for the prevention of many cancers. This is the subject of intense research
- The identification of the environmental factors that cause mutations in other 'cancer protection' genes over the individual's lifetime that eventually lead to melanoma are also unknown although it is clear that melanoma increases with sun exposure, where an individual has a number of moles, and if they are fair-skinned

### What are the inherited faulty 'cancer protection' genes involved in predisposition to melanoma?

There are a number of 'cancer protection' genes in which inherited changes that make the genes faulty (mutations) can contribute to a melanoma developing (see Figure 50.1).

Two of the genes that have been identified are called:

- **CDKN2A** which contains the information for the cells to make proteins (called P16 and P14) which have a central role in controlling the process of cell growth and division
  - Mutations in the CDKN2A gene have been found in approximately 20%-50% of families in different populations with three or more melanoma affected first-degree relatives
- **CDK4** which has been found in fewer families

All men and women have two copies of the CDKN2A and CDK4 genes in their cells and the role of these genes is 'cancer protection'.

There are also a number of families where it is clear from the family history that members are at potentially high risk for having an inherited predisposition to melanoma, but where mutations in the CDKN2A and CDK4 genes cannot be found:

- It is likely that there are a number of yet unidentified genes in which mutations predispose to melanoma
- Research is continuing to try to identify these genes and their function
- Genetic testing may not identify all possible gene changes

### Figure 50.1: Proportion of cases of melanoma that involve an inherited predisposition (susceptibility).

Only 1% to 2% of cases of melanoma involve inherited predisposition.
The indicators that melanoma in a family could be due to an inherited mutation include:

- Three or more 1° or 2° relatives with melanoma
- Several primary melanomas in one person
- Young age of onset of the first melanoma (less than 40 years)
- The presence of atypical or unusual moles early in life
- These families would be candidates for participating in research programs where genetic testing for mutations in candidate genes may be performed

Can an individual determine if they have inherited a faulty CDKN2A or CDK4 gene copy?

People with a strong family history like that described above can seek advice from their local genetic counselling service or a specialist family cancer clinic (if available). Their risk of developing melanoma, based on their family history, can be estimated and discussed in more detail (see Genetics Fact Sheet 3).

Genetic counselling team may be able to:

- Clarify their chance of developing melanoma based on their family history
- Answer any questions they may have about their family history of cancer
- Discuss what medical check-ups are appropriate
- Discuss the limitations, potential benefits, disadvantages and appropriateness of genetic testing (see Genetics Fact Sheet 21)

Genetic testing for mutations in the genes for melanoma is still largely in the research setting. It is complex and involves

- **First**, identifying the mutation in a family member who has or had melanoma. This is called a *mutation search* and may take considerable time.
- **Second**, and only if a mutation is found, testing other family members to determine if they have inherited the faulty gene. This is called *predictive genetic testing* (see Genetics Fact Sheet 21).

What can be done if an individual has an inherited predisposition to melanoma or is at potentially high risk for developing the condition?

All individuals with a strong family history of melanoma or where a faulty CDKN2A or CDK4 gene has been identified in their family can seek advice from a specialist family cancer service (if available) or their local genetic counselling service. The risk for an individual developing melanoma, based on their family history, can be estimated and discussed in more detail (see Genetics Fact Sheet 3).

Checking for melanosomas should be arranged in association with the familial cancer service, and discussions will include:

- Education about sun protection and early detection
- Intensive surveillance, commencing from age 10, including:
  - Three-monthly self-examinations
  - Whole-body photography
  - Skin surface microscopy as a baseline
  - Skin and scalp examination by a dermatologist, six or twelve-monthly

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 3, 4, 5, 9, 21, 47, 48, 49, 51

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