

This Fact Sheet describes when melanoma is considered to be a familial condition. A small number of families have an increased chance of developing cancer because of an inherited faulty gene in the family. This is known as an inherited predisposition to cancer.

In summary

- **Melanoma is very common, especially in Australia, and mostly occurs just by chance**
- **Some rare families have inherited a faulty gene that can increase the likelihood of some individuals developing melanoma**
- **There are a number of factors which can influence an individual's chance of developing melanoma, one of which is having a family history of the condition.**

WHAT IS MELANOMA?

Melanoma is a type of skin cancer which usually develops when moles become cancerous. In Australia, about 1 in 18 (5.5%) people will develop melanoma by the age of 85 years. 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.

Melanoma can occur anywhere on the skin— 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 and in women, on the lower legs.

Melanocytes are the pigment cells in the skin 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. When clusters of melanocytes and surrounding tissue form benign (non-cancerous) growths they are called moles. Moles are also referred to as 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.

However, often, but not always, melanoma occurs when the melanocytes in a mole become cancerous.

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

WHAT CAUSES MELANOMA?

There is no single cause. There are a number of risk factors which can influence an individual's chance of developing 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 means having one or more close blood relatives who have, or have had, melanoma. Relatives could be on **either the father's or the mother's side** of the family, but not added together.

The closest blood relatives (not relatives by marriage) are parents, siblings and children and are called first-degree relatives.

Aunts, uncles, nephews, nieces and grandparents are second-degree relatives.

A family history of melanoma can be due to:

- Chance, because cancer is common
- Common environmental and lifestyle influences among family members (for melanoma these include high sun exposure or having the same skin colouring)
- Having a faulty 'cancer protection' gene in the family.

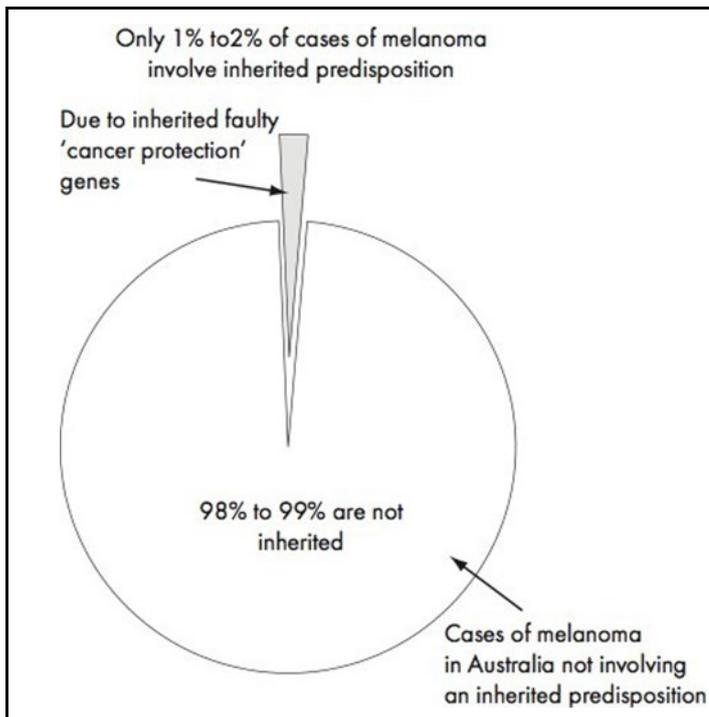


Figure 34.1: Proportion of cases of melanoma that involve an inherited predisposition (susceptibility).

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 small number will have a potentially high chance of developing melanoma because their family has an inherited predisposition to this cancer.

INHERITED PREDISPOSITION TO DEVELOPING MELANOMA

Most melanoma cases are not due to an inherited predisposition.

However a very small number (estimated at less than 1%-2%) of the cases of melanoma in Australia involve an inherited predisposition to develop the cancer (*Figure 34.1*). In these cases, the individuals have inherited a faulty copy of a melanoma 'cancer protection' gene.

Cancer occurs when cells in the body continue to divide uncontrollably. This can happen in any tissue or organ in the body. A group of cells that has resulted from uncontrolled cell division and growth is called a tumour.

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.

Variations to the information in one of these 'cancer protection' genes such as a skin pigment cell (melanocyte) may cause the process of cell division to be less well controlled and cells may grow and divide abnormally. A variation that makes the gene faulty is called a **mutation** or a **pathogenic variant**.

The cycle of cell division and growth continues throughout the lifespan and mutations can build up over this time. Mutations have to occur in a number of different 'cancer protection' genes in a cell, building up over time, before that cell becomes cancerous. This is why the development of melanoma occurs in younger adults or can take years.

The reason why these mutations occur is thought to be a combination of genetic factors, environmental factors and the process of ageing. Research is currently being undertaken to more fully understand the cause of specific gene mutations.

For the small number of people that have inherited a mutation in a 'cancer protection' gene the division and growth of melanocytes is not as tightly controlled as in other people in the population.

One way of representing this process is to think of the path to cancer as a staircase where the bottom of the staircase represents a normal cell and the top a cancerous cell (*Figure 34.2*).

The steps of the staircase represent a progression of changes to the information that may occur in one or both copies of a number of different 'cancer protection' genes in a cell. Some of these changes will be mutations.

So for a normal cell to become cancerous, both copies of a number of different 'cancer protection' genes in the cell of a tissue or organ must become faulty over time.

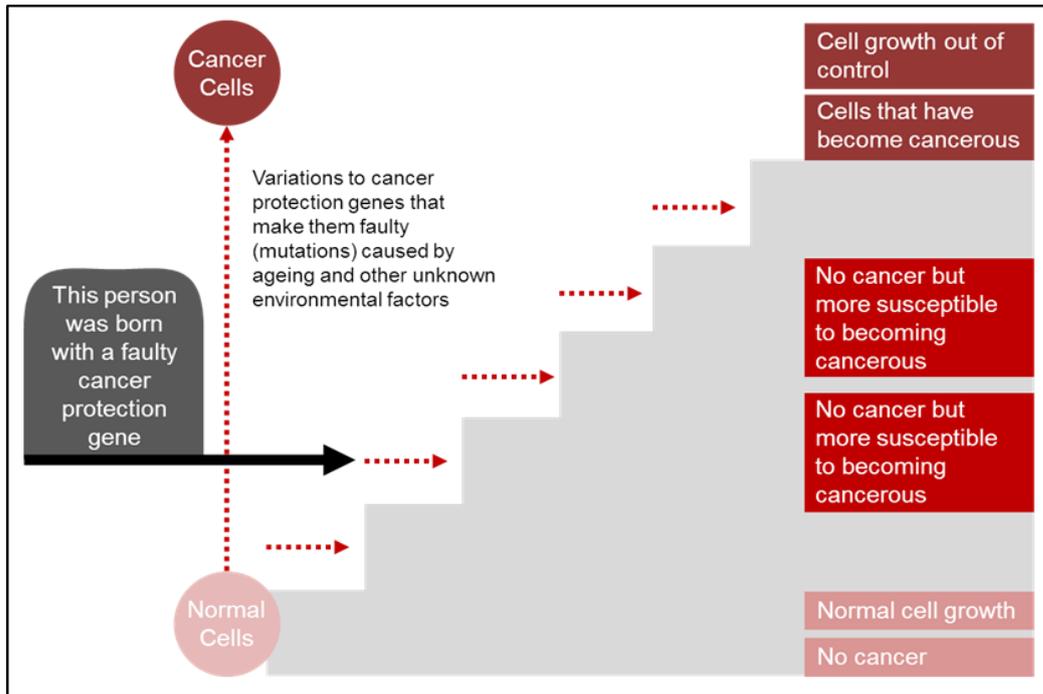


Figure 34.2: Changes build up in the different ‘cancer protection’ genes in the cells over time due to ageing and other environmental factors. Some of these changes make the ‘cancer protection’ genes faulty. Each step on the staircase to becoming cancerous cells represents a change in a copy of one of the many ‘cancer protection’ genes in the cells.

If a person is born with a mutation in one of the ‘cancer protection’ genes, they are already on the first step of the staircase (Figure 34.2). Their chance of developing melanoma is higher than average but unless further mutations occur over time in a number of other ‘cancer protection’ genes, those cells will never become cancerous.

It is thought that not just one but many gene changes are associated with the development of melanoma.

WHAT ARE THE INHERITED FAULTY ‘CANCER PROTECTION’ GENES THAT CAUSE MELANOMA?

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.

There are a number of ‘cancer protection’ genes in which inherited mutations can contribute to a melanoma developing.

Two of the genes that have been identified are:

- *CDKN2A* gene (Cyclin-dependent kinase inhibitor 2A)
- *CDK4* gene (Cyclin- dependent kinase 4).

The *CDKN2A* and *CDK4* genes provide instructions for making proteins that play a role in cell division and growth.

CDKN2A ‘cancer protection’ gene is known as a tumour suppressor gene and its role is to act as the ‘brakes’ on uncontrolled cell growth. *CDK4* provides instructions for making a protein (kinase) that is part of the cell division and growth cycle.

Mutations in the *CDKN2A* gene have been found in approximately 20%- 50% of families in different populations with three or more people in the family with melanoma and also in families with a history of pancreatic cancer. *CDK4* mutations have been found in fewer families.

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. There have been some genes identified that are associated with melanoma susceptibility but result in a small to moderate increase in risk of melanoma. Research is continuing to try to identify the impact of these genes in combination and to identify new genes and their function.

WHAT IS THE PATTERN OF INHERITANCE IN FAMILIES WITH A FAULTY *CDKN2A* OR *CDK4* GENE?

CDKN2A or *CDK4* gene mutations are inherited in an autosomal dominant pattern (Figure 34.3).

This is because:

1. The *CDKN2A* and *CDK4* genes are located on the autosomes (numbered chromosomes) called chromosome 9 and 12 respectively.
2. The effects of mutations in the *CDKN2A* or *CDK4* genes are **dominant** over the information in the working copy of the genes.

Where one of the parents has a *CDKN2A* or *CDK4* gene mutation, in every pregnancy each of their children has

- 1 chance in 2 (50% chance) of inheriting the gene mutation
- 1 chance in 2 (50% chance) of *not* inheriting the gene .

A *CDKN2A* or *CDK4* gene mutation can be inherited from either the mother or the father and passed on to either a son or daughter.

People who have not inherited a faulty gene are not at increased risk of developing melanoma over their lifetime and cannot pass the faulty gene on to their own children. However, they still have the same risk for developing melanoma as the average person in the Australian population.

WHAT ARE THE CLUES IN A FAMILY HISTORY OF MELANOMA?

Documenting the health history of family members over several generations helps determine if a person has a strong family history. It is important to record how the individual is related, the type of cancer they have or had and the age of the individual when cancer was first diagnosed.

A strong family history of melanoma may mean an inherited gene mutation is present in the family. This usually includes one or more of the following:

- Two close relatives with melanoma

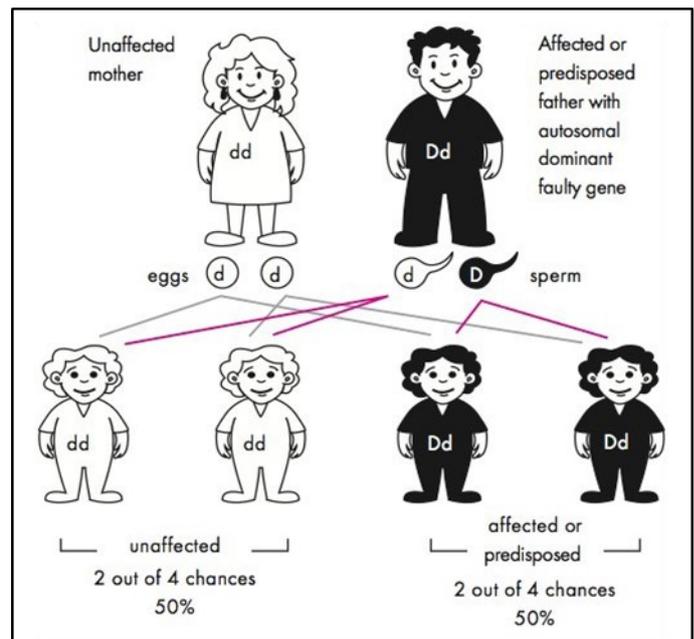


Figure 34.3: Autosomal dominant inheritance when one parent has a faulty gene copy. The faulty gene is represented by 'D'; the working copy by 'd'.

- Two relatives with melanoma (even if distant relatives) if one or more have had multiple primary cancers or they have the atypical mole syndrome (dysplastic nevi)
- Three or more cases of melanoma in a family

People with a strong family history can be referred by their doctor to a specialist family cancer service or their local genetic counselling service.

GENETIC COUNSELLING AND TESTING

The genetic counselling team may be able to:

- Clarify the chance of developing melanoma based on a person's family history
- Answer any questions about the family history of cancer
- Discuss the limitations, potential benefits, disadvantages and appropriateness of genetic testing
- Discuss cancer screening and risk reducing strategies.

<i>Genes associated</i>	Chance (risk) for people developing melanoma up until age 80 years	Chance (risk) for people developing pancreatic cancer up until age 80 years
<i>CDKN2A</i>	52% ¹	17%

Table 34.1: Chance of developing melanoma and pancreatic cancer for people with a *CDKN2A* gene mutation

Reference: 1. Cust, A. E., M. Harland, E. Makalic, et al. 2011. "Melanoma risk for *CDKN2A* mutation carriers who are relatives of population-based case carriers in Australia and the UK." *J Med Genet* 48(4):266-272.

Genetic testing for mutations in the *CDKN2A* and *CDK4* genes is complex and involves:

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

Genetic testing, however, for mutations genes associated with melanoma is still largely in research.

WHAT IS THE CHANCE OF DEVELOPING MELANOMA AND OTHER CANCERS?

People with a *CDKN2A* gene mutation have an increased chance of developing melanoma and a moderate chance of developing pancreatic cancer. People with a *CDK4* mutation have an increased chance of developing melanoma- further trials are needed to clarify the risk (*Table 34.1.*)

MANAGING AN INCREASED RISK OF DEVELOPING MELANOMA DUE TO A *CDKN2A* OR *CDK4* GENE MUTATION

Discuss your family health history with your doctor

Many cancers can be cured if picked up at the earliest stage. Discuss your personal and family history of cancer with your GP.

Genetic counselling and risk management

It is recommended that people with a *CDKN2A* or *CDK4* gene mutation and their relatives, seek management advice from a genetic service, a family cancer clinic or medical specialist.

Screening is important

The earlier a cancer is found, the more successful the outcome of treatment is likely to be. Checking for melanomas includes:

- 6 - 12 monthly specialist dermatological total body skin examination from puberty including scalp and genitalia
- monthly self-examination from puberty
- photographic records of naevi (moles).

Lifestyle and skin cancer prevention behaviours can make a difference

The progression to melanoma requires mutations to build up in a number of the 'cancer protection' genes in the cells over time. The reason why these mutations occur is thought to be a combination of genetic factors, environmental factors and the process of ageing. Research is currently being undertaken to more fully understand the cause of specific gene mutations.

However, it has shown that skin cancer prevention behaviours that include avoiding sunburn, wearing sunscreen, a shirt with sleeves, a hat, and sunglasses, seeking shade and reducing time spent outdoors during peak hours of ultraviolet radiation will reduce the chance of developing melanoma.