Fact sheet **34**

MELANOMA & INHERITED SUSCEPTIBILITY

This Fact Sheet talks about when melanoma is considered to be a hereditary or familial condition. A small number of families have an increased chance of developing cancer because they have inherited a DNA change in a cancer protection gene.

IN SUMMARY

- Melanoma is common, especially in Australia, and mostly occurs just by chance
- A small proportion of families have an inherited susceptibility to developing melanoma
- There are a number of factors which can influence a person'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 20 (5%) people will develop melanoma by the age of about 80 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.

When skin is exposed to the sun, the skin produces more pigment, causing the skin to tan, or darken. When these spots and surrounding tissue form benign (non-cancerous) growths they are called moles. Moles are also referred to as naevus; the plural is naevi. Most moles will remain benign (harmless) and not develop into melanoma.

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 for melanoma. There are, however, several risk factors which can influence someone's chance of developing melanoma. The most important are:

- Sun exposure
- The number of moles a person has
- The colour of a person'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.

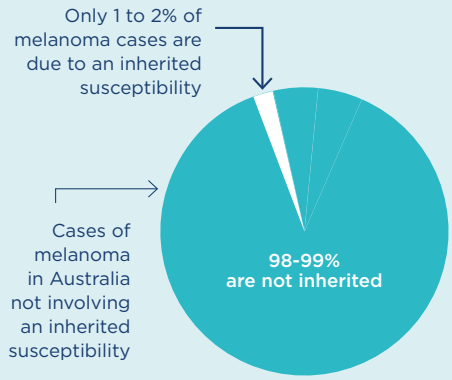
WHAT IS MEANT BY A FAMILY HISTORY OF MELANOMA?

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 usually 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.

Content updated November 2021
NOV21/V1 NS12673
SHPN: (HETI) 240981

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



A family history of melanoma can be due to:

- Chance, because cancer is common
- Common environmental and lifestyle influences among family members (including where a family lives, sun exposure and lifestyle).
- Having shared genetic factors, such as having the same skin colouring. Inherited risk may also be due to a non-working 'cancer protection' gene in the family.

Not everyone with a family history of melanoma is at increased risk. Many people will know of a relative who has had melanoma, just because melanoma is common in Australia. Such people may still be only slightly above the average risk. Where a number of their close blood relatives have been affected with melanoma and, or they were diagnosed at a young age, a person's risk of developing melanoma may be at moderately increased or potentially high risk.

CELLS, DNA AND GENES

Our bodies are made up of billions of cells. Each cell contains a complete copy of our genetic information or DNA. Our DNA contains the instructions for growth and development and is packaged into chromosomes that contain all our genes. Genes provide a code for the proteins our body needs to function.

We all have two copies of every gene, one that is inherited from the mother, and one from the father. As we age and grow, our cells are continually dividing to form new cells by the process of cell division. This means our DNA is copied over and over again.

INHERITED SUSCEPTIBILITY TO MELANOMA

Most melanoma cases are not due to an inherited susceptibility.

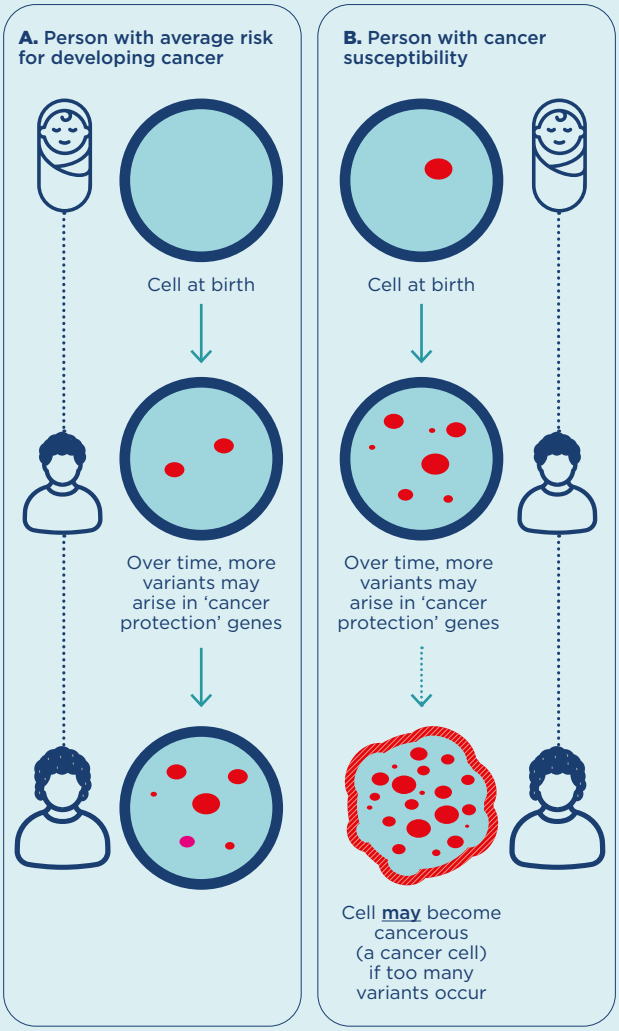
However a very small number (estimated at less than 1%-2%) of the cases of melanoma in Australia involve an inherited non-working copy of a cancer protection gene. A spelling mistake in the gene that stops it working properly is called a **pathogenic variant** or **mutation**.

Pathogenic variants in these cancer protection genes may cause cells to grow and divide in an uncontrolled way. For a cell to become cancerous, multiple variants have to build up in a number of different 'cancer protection' genes within a cell over time.

It can take many years for a cancer to develop, and this is the reason why the risk of cancer increases with age and most cancers occur in older people. The reason why these variants occur is thought to be a combination of genetic factors, environmental factors and the process of ageing.

Figure 34.2 shows a stylised image of a cell from a person with average risk of developing cancer (left hand side) and the cell of someone with an inherited pathogenic variant at birth (right hand side). Over time, as we age, we accumulate variants in genes that may increase the 'burden' or risk for developing cancer. If enough of these variants arise over time, the cell becomes cancerous (a 'cancer cell'). The person with the inherited pathogenic variant is more likely to have a cancer develop in their lifetime, because their cells started with a pathogenic variant already present at birth. This means that fewer variations need to happen to the cells' protective genes for a cancer to develop.

Figure 34.2:
Increased chance of cancer cell development in those born with a cancer susceptibility compared with the average person



WHAT IS A 'STRONGER' FAMILY HISTORY THAT SUGGESTS AN INHERITED SUSCEPTIBILITY?

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 when cancer was first diagnosed. A strong family history of melanoma may mean an inherited gene variant is present in the family.

Characteristics of a family that may suggest an inherited pathogenic variant include:

- Two close relatives with melanoma
- 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 medical specialist or family cancer service.

WHAT ARE THE 'CANCER PROTECTION' GENES THAT CAUSE AN INCREASED RISK OF MELANOMA WHEN NOT WORKING?

There are a number of 'cancer protection' genes in which inherited variants can increase the risk of melanoma.

One important gene that has been identified is:

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

The *CDKN2A* gene provides instructions for making proteins that play a role in cell division and growth.

The *CDKN2A* 'cancer protection' gene is known more specifically as a tumour suppressor gene and its role is to act as the 'brakes' on uncontrolled cell growth. Variants in other genes, for example *CDK4* have been identified in some rare cases, however further research is needed on the implications they have for families.

Pathogenic variants 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.

Many families may have a strong history of melanoma without an identifiable mutation. It is likely that there are a number of yet unidentified genes in which pathogenic variants increase the chance for melanoma. Research is continuing to study the effects of other genes and to identify new genes.

HOW IS A *CDKN2A* GENE VARIANT INHERITED?

CDKN2A gene variants are inherited in an autosomal dominant pattern (*Figure 34.3*).

This is because:

1. Each person carries two copies each of the *CDKN2A* gene, one inherited from their mother, one from their father.
2. The effects of a pathogenic variant in the *CDKN2A* gene is **dominant** over the information in the working copy of the gene.

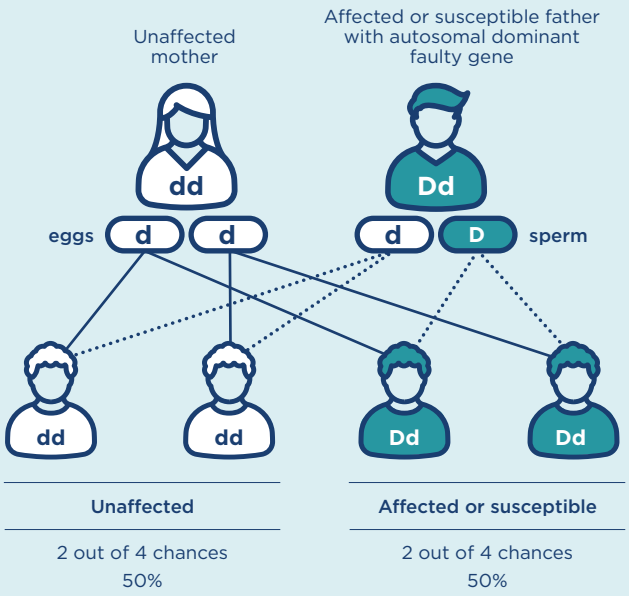
Where one parent has a *CDKN2A* gene variant, in every pregnancy each of their children has

- 1 in 2 (50%) chance of inheriting the pathogenic gene variant
- 1 in 2 (50%) chance of not inheriting the gene variant and inheriting a working copy of the gene from both parents.

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

People who have not inherited the pathogenic variant cannot pass it on to their children. However, they may still have an increased risk for developing melanoma above the average person in Australia, based on other risk factors that they have.

Figure 34.3:
Autosomal dominant inheritance when one parent has a non-working *APC* or *MMR* gene . The non-working gene is represented by 'D'; the working copy by 'd'.



GENETIC COUNSELLING AND TESTING

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

The genetic counselling team may be able to:

- Work out the chance of developing melanoma based on a person's family history
- Work out whether genetic testing is likely to be helpful
- Talk about the limitations, potential benefits and disadvantages of genetic testing
- Talk about cancer screening and risk reducing strategies.

Genetic testing for pathogenic variants in the *CDKN2A* gene is complex and involves:

- First identifying the gene variant via a blood sample in a family member who has or had melanoma (a **variant search**). A variant search is sometimes performed on a group of selected genes (known as a panel). This group may include some different genes depending on the cancer types present in the family.

Results can be:

1. The pathogenic variant was found
2. No pathogenic variant was found
3. A variant of uncertain significance (VUS) was found. This is an unclear result. Further information to understand different types of results is available at www.genetics.edu.au.

- Then, and only if a pathogenic variant is found, testing other family members to determine if they have inherited the same variant (**predictive genetic testing**).

Table 34.1:
Chance of developing melanoma and pancreatic cancer for people with a *CDKN2A* pathogenic variant. Information extracted from eviQ Risk Management Guidelines.

Genes associated	Chance (risk) for people developing melanoma up until age 80 years	Chance (risk) for people developing pancreatic cancer up until age 80 years
CDKN2A	52%	Uncertain but increased in some populations
General Population Risk	About 5% but varies somewhat by state	About 1%

WHAT ARE THE CHANCES OF DEVELOPING MELANOMA FOR SOMEONE WHO HAS A PATHOGENIC VARIANT IN *CDKN2A*?

People with a pathogenic variant in *CDKN2A* have an increased chance of developing melanoma and pancreatic cancer (*Table 34.1*). People with a *CDK4* pathogenic variant have an increased chance of developing melanoma but the exact risk is unclear.

WHAT CAN BE DONE TO MANAGE AN INCREASED RISK OF MELANOMA DUE TO A *CDKN2A* PATHOGENIC VARIANT?

Genetic counselling and risk management

It is recommended that people with a *CDKN2A* gene variant and their relatives, seek management advice from a family cancer clinic or medical specialist. National guidelines for practitioners exist at the Cancer Institute NSW eviQ website.

Screening is important

The earlier a cancer is found, the more successful the outcome of treatment is likely to be. All people should be aware of any unusual changes in their skin or moles. For people at increased risk, checking for melanomas includes regular self-examination and skin checks with a specialist.

Lifestyle and skin cancer prevention behaviours can make a difference

Most cancers occur due to a combination of genetic factors, environmental factors and the process of ageing.

Sun protective behaviours that include avoiding sunburn, wearing sunscreen, a shirt with sleeves, a hat, sunglasses, seeking shade and reducing time spent outdoors during peak hours of ultraviolet radiation will reduce the risk of melanoma. Maintaining a balanced diet high in fibre and low in fat, no smoking and living a healthy lifestyle can reduce the chance of developing other cancers.

More support and information is available for individuals and families through support organisations including Melanoma Patients Australia, Cancer Council and Genetic Alliance Australia.