



Cancer is unregulated cell growth which may result in tumours developing. These can become malignant, and invade and spread to other parts of your body.

Skin cancer is cancer of skin cells. There are three main types:

- melanoma: skin cancer arising from melanocytes: skin pigment cells;
- squamous cell carcinoma: skin cancer arising from epithelial cells (outermost layer of the skin); and
- basal cell carcinoma: skin cancer arising from basal cells (inner layer of the skin).



Melanoma (left), squamous cell carcinoma (middle), basal cell carcinoma (right) © Cancer Council of Western Australia

Melanoma arises from melanocytes; these cells produce melanin, the pigment responsible for skin, hair and eye colour. Each year melanoma accounts for 10% of all cancer diagnoses within Australia, and 2% of all skin cancers.

Australia has one of the highest rates of melanoma in the world, with over 11 500 people diagnosed every year, and 1500 dying annually.

Melanoma usually develops on skin, but rare forms can develop in the eyes and mucosal membranes, including mouth, sinuses and urogenital tract.

Metastatic melanoma

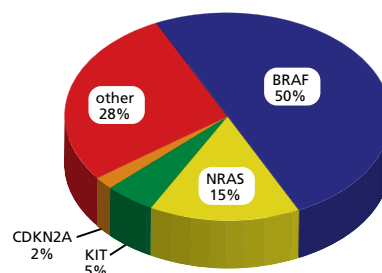
Melanoma detected early is considered treatable, usually by surgical removal. However, if melanoma spreads (metastasises) to other parts of the body through the lymphatic or circulatory system, it's almost always incurable.

Treatment options for metastatic melanoma include traditional cancer therapies, such as: chemotherapy, radiotherapy and immunotherapy. However, melanoma is considered one of the most difficult cancers to treat, as it's relatively resistant to many traditional treatments. Median survival rate for patients with advanced metastatic melanoma is low: 8 – 9 months.

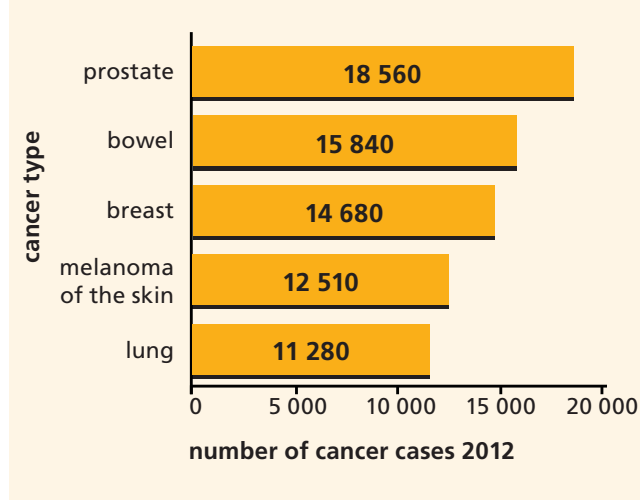
Genetics of melanoma

Melanoma, like all cancers, is the result of genetic mutations. Mutations can be inherited or acquired over a person's lifetime. Approximately 25 000 genes make up the human genome. Of these, scientists have identified a number commonly associated with melanoma. Advances in biotechnology have made it possible for scientists to sequence melanoma genomes and to develop treatments that target a number of key mutations common to the disease.

Prevalence of common melanoma mutations



Estimated five most commonly diagnosed cancers in Australia, 2012



Acquired gene mutations

Somatic mutations, acquired over a person's lifetime, are associated with most melanomas. These acquired mutations aren't the result of a single factor, but certain risk factors (such as sun exposure) are associated with an increased risk of melanoma developing.

Genetic sequencing reveals several common acquired mutations in melanoma tumours.

New treatments focus on these mutations.

The protein products of the three genes discussed below: BRAF, NRAS and KIT, are part of cell-signalling pathways that control the cell cycle. Mutations acquired in these genes may cause significant changes to gene expression within the cell.

BRAF mutation

Acquired BRAF mutations are found in approximately 50% of melanoma tumours and around 8% of all cancer tumours. There are a number of mutation variants but the most common in melanoma is V600E. This mutation involves a single nucleotide change: thymine (T) to adenine (A), resulting in a single amino acid change in BRAF protein: valine to glutamic acid. (V is the abbreviation for valine; E is the abbreviation for glutamic acid; 600 refers to the position of the amino acid mutation).

BRAF gene codes for BRAF protein, which plays an important role in the cell-signalling pathway involved in cell growth, cell differentiation, and cell death. Under normal circumstances BRAF protein is only active when signalled by molecules in the MAPK cell-signalling pathway.

Mutated BRAF gene results in production of mutant BRAF protein. Mutant BRAF protein is continuously active, independent of the cell-signalling pathway. Mutant BRAF activates the next protein in the cascade: MEK, which in turn signals ERK. The result is continual cell growth and proliferation. This abnormal activation of the MAPK cell-signalling pathway leads to changes in gene expression within the cell.

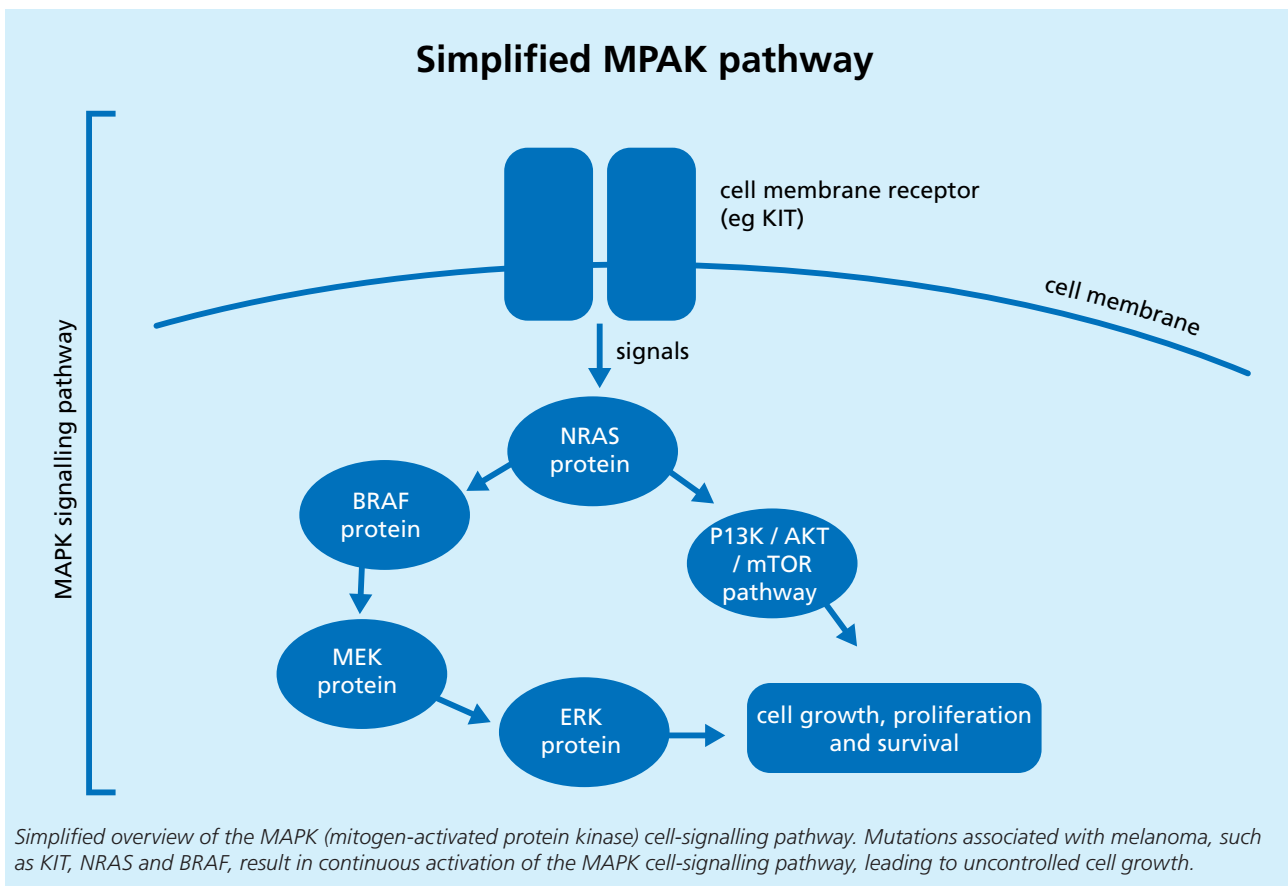
On its own, the BRAF V600E mutation isn't considered sufficient to cause melanoma. Other mutations are also involved.

A high proportion of BRAF mutations associated with metastatic melanoma has led to the development of mutant BRAF inhibitor treatments. These drugs have been successful in blocking the action of mutated BRAF protein, halting continual activation of the MAPK cell-signalling pathway, and causing cancer cell death.

NRAS mutation

Around 15 - 25% of melanomas harbour mutations in the NRAS gene. NRAS mutations often involve single nucleotide substitutions in random positions on the gene which result in single amino acid change in the gene's protein product. Mutant NRAS produces mutant NRAS protein, which, like BRAF, activates cell-signalling pathways, resulting in continual cell growth and division.

Normal NRAS protein is involved in regulating cell division, and is active in MAPK and P13K cell-signalling pathways. NRAS mutations are associated with a number of cancers including: melanoma, thyroid and myeloid leukaemia.



NRAS mutations aren't associated with any single risk factor, but there's evidence melanomas, originating from chronic sun-damaged skin, may be more likely to harbour NRAS mutations. In order to treat melanoma patients with NRAS mutations, a number of clinical trials combining various inhibitor drugs that target the MAPK cell-signalling pathway are underway.

KIT mutation

Around 2 – 6% of acquired melanomas harbour mutations in the KIT gene. This gene produces KIT protein that activates various cellular pathways involved in cell growth and division, cell survival and cell motility. A number of KIT mutations that produce faulty KIT protein have been identified. Mutant KIT proteins can act independently, like BRAF, activating downstream cell-signalling pathways, leading to cell growth and proliferation.

Mutations in the KIT gene are most common in acral and mucosal melanomas, and melanomas originating from chronic sun-damaged skin.

- Acral melanomas occur on the soles of feet, palms of hands and under fingernails. This melanoma type is rare in Caucasians, but is the most common type observed in those with darker skin.
- Mucosal melanomas occur in mucosal linings of the body: largely the mouth, sinuses and urogenital tract. This type is rare, less than 5% of all melanomas.

Mutant KIT is observed in a number of cancers including: melanoma, gastrointestinal stromal tumour and myeloid leukaemia. Drug treatments that target mutated KIT protein have successfully treated gastrointestinal stromal tumours and are currently being trialled in melanoma patients.

Inherited gene mutations

Inherited predisposition for melanoma is rare. In Australia, germline mutations account for only 1 – 2% of all melanomas. Usually, when a family history of melanoma is observed it's due to chance, or because family members share similar environments and phenotypic traits, such as skin type.

CDKN2A mutation

Inherited changes to the CDKN2A gene are found in 20 – 50% of families with a history of melanoma. Familial melanoma due to this inherited mutation is associated with:

- three or more first or second-degree relatives with melanoma;
- multiple primary melanomas in one individual; and
- melanoma developing at a young age, less than 40 years.

CDKN2A is a tumour suppressor gene playing an important role in regulating cell division and growth. Mutations of CDKN2A often result in the loss of tumour-protecting functions of its protein products: p16 and p14. These mutations are found in a number of cancers including melanoma, pancreatic and gastric.

The pattern of inheritance in familial melanoma is autosomal-dominant. Children with a parent carrying mutant CDKN2A gene have at least a 50% chance of inheriting this faulty gene. A single mutation in CDKN2A isn't considered enough to cause melanoma, but those carrying this mutation are at increased risk.

All melanomas are associated with genetic mutations, inherited or acquired. Acquired mutations are influenced by environmental factors, such as geography and sun exposure patterns, as well as phenotypic traits, such as skin type.

The accumulation of genetic mutations leads to the development of melanoma. Most melanomas are associated with mutations in key cell-signalling pathways active in cell division, growth and proliferation. These mutations result in melanoma cells developing different gene expression patterns that involve overexpression, underexpression and silencing of related genes and their protein products.

With the advent of new genetic sequencing technologies scientists are moving toward molecular classification of melanoma. The genetic profile of a melanoma tumour can be sequenced to determine which genes, and cell-signalling pathways, are affected. These discoveries have led to development of new targeted treatments that extend patient lifespan.