

Melanoma and the MAP2K1 P124L Mutation

This material will help you understand:

- the basics of melanoma
- the role of the MAP2K1 gene  in melanoma
- if there are any drugs that might work better if you have certain changes in the MAP2K1 gene

What is melanoma?

Melanoma is a type of skin cancer. It starts in the cells that make melanin, the substance that gives skin its color.

What causes melanoma?

Cancer is caused by changes in our genes . Genes contain the instructions for making proteins . Changes in genes, called mutations , may result in changes in proteins. These changes may cause cells to grow out of control which could lead to cancer.

Melanoma usually starts on areas of the skin exposed to the sun. But melanoma can also show up in other parts of your body like the eye, the bottom of the feet, under the nails, or inside the mouth.



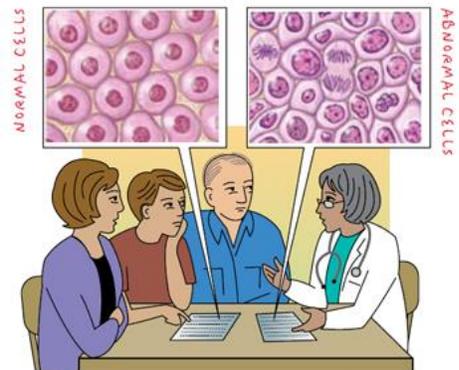
What are the most common current treatments for melanoma?

Doctors may treat melanoma using one or more of these options:

- **Surgery** – operation that removes as much of a cancer tumor as possible.
- **Traditional chemotherapy** – drugs that kill growing cells. All cells grow, but cancer cells grow faster than healthy cells. So, these drugs kill more of the cancer cells. But because these drugs kill healthy cells too, this can cause unwanted side effects.
- **Precision medicine therapy** – treatments that target proteins  involved in cancer.

These therapies mainly kill cancer cells and not healthy cells. This also means you may have fewer side effects. Two types of precision medicine therapies are:

- **Small molecule therapy** – mainly acts on cells with specific protein changes. Small molecule therapy uses drugs to target those proteins. Genetic testing  can tell if your cancer cells have protein changes that can be targeted. Small molecule therapy is a type of targeted therapy .
- **Immune-based therapy** – works with your body's defense system to fight cancer. These can mark cancer cells so they are easier for your immune system  to find.



Can I pass on mutations found in my cancer cells to my children?

You cannot pass on mutations found only in your cancer cells to your children.

How well does cancer drug treatment work?

After a while, your cancer cells may stop responding to the drug(s). This means your cancer may start to grow again. Your doctor will do regular checkups to watch for this. If the cancer starts to come back, your doctor can try another drug or treatment.



What is MAP2K1?

MAP2K1 (pronounced “Măp-2-K-1”) is a shorthand name for both the MAP2K1 gene and protein. The MAP2K1 gene contains the instructions for making the MAP2K1 protein. MAP2K1 is a member of the MAPK family of proteins. Their main job is to help control cell growth. They are part of a pathway. Proteins in pathways work together to do specific jobs within the cell. Some of the other proteins in this pathway include RAS, RAF and ERK (Figure 1). This pathway is a signaling pathway. It passes signals from outside the cell to the cell’s nucleus. The nucleus is the control center of the cell. These signals may tell the cell to grow, divide, or die. These are all normal cell functions. The body turns the signals on and off as needed.

What is MAP2K1’s role in the growth pathway?

In healthy cells, the growth signal turns proteins “on.” As the signal reaches each protein in the pathway, it turns on the protein. The RAF protein receives the signal via RAS. RAF passes it on to MAPK, and MAPK passes it on to ERK. ERK is the last protein in the pathway. When ERK is on, it turns on genes in the nucleus that help cells grow. When the signal stops, the proteins turn off.

How do mutations in proteins affect pathways?

If a mutation affects one or more proteins in a pathway, the proteins may not be able to be turned on or off as expected. This can cause cells to grow out of control and lead to cancer.

How common are MAP2K1 mutations in melanoma?

Less than 1 in 10 melanomas have a mutation in the MAP2K1 gene that changes the MAP2K1 protein. MAP2K1 mutations are most common in melanomas found on skin damaged by the sun. But these mutations can occur in all types of melanoma. Cancer cells with mutations in MAP2K1 also tend to have mutations in the BRAF or NRAS gene.

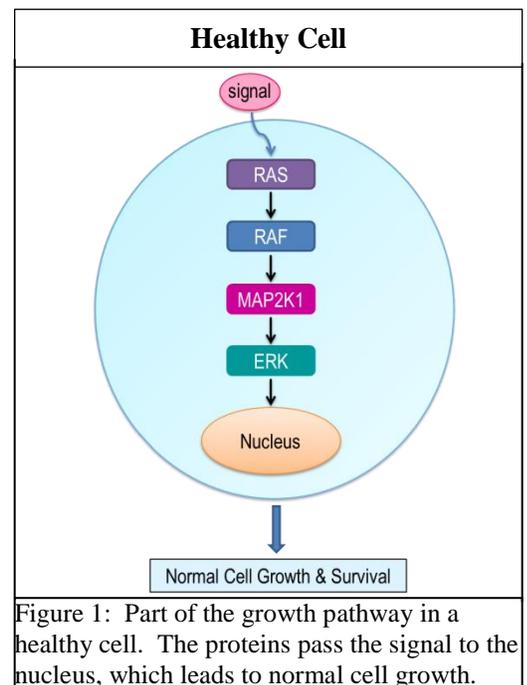
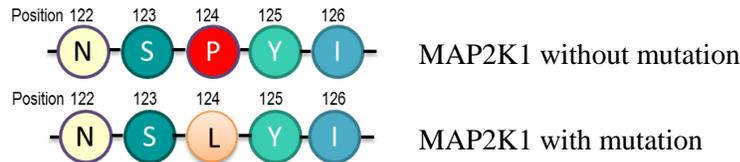


Figure 1: Part of the growth pathway in a healthy cell. The proteins pass the signal to the nucleus, which leads to normal cell growth.

What is the MAP2K1 P124L mutation?

MAP2K1 P124L is a specific variation in the MAP2K1 protein. Proteins are long chains of amino acids. The MAP2K1 protein has 393 amino acids. MAP2K1 with no mutation at amino acid position 124 has a proline, or P for short. The amino acid at position 124 in MAP2K1 with the P124L mutation is a leucine, or L for short.



What is the effect of this mutation?

The P124L mutation is in the part of MAP2K1 that passes along the cell growth signal. Currently, we do not know how this mutation is related to cancer.

Are there targeted therapies for MAP2K1 P124L?

Targeted therapies for MAP2K1 do not work well for this mutation. Targeted therapies usually stop MAP2K1 from passing along the signal. But cells with MAP2K1 P124L can still pass along the signal even when the drug is present. At this time, it is unclear if any drugs target MAP2K1 with this specific mutation. But, you should talk to your doctor about your treatment options.

What if I have a different mutation in MAP2K1 or “no mutation”?

You might still have other mutations in this gene or in other genes that were not tested. Your genetic test results will still help your doctor determine the best treatment for you.