

Melanoma and the GNAQ Q209L Mutation

This material will help you understand:

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

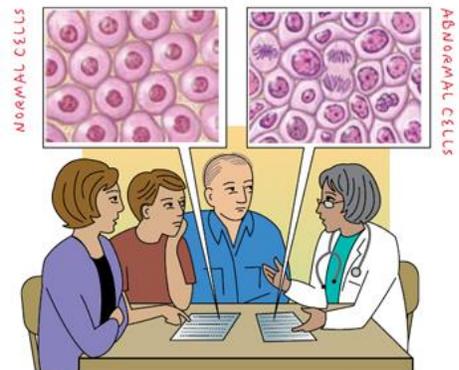
Doctors may treat melanoma using one or more of these options:

- **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.

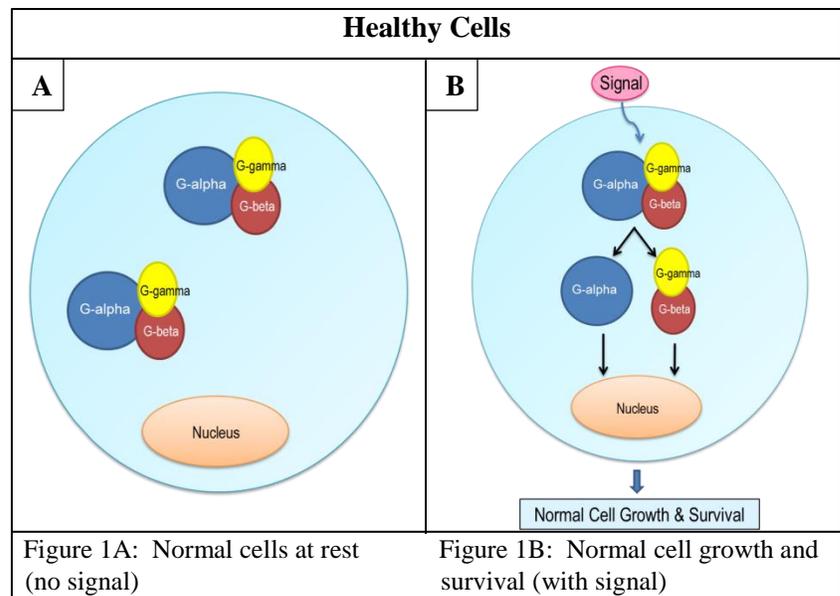


What is GNAQ?

GNAQ is the gene that contains the instructions for making the GNAQ protein. GNAQ combines with two other proteins to form a “G protein.” G-alpha, G-beta, and G-gamma are general names for the proteins. GNAQ is a G-alpha protein. It is also referred to as G-alpha-q.

G proteins help pass signals from outside the cell to inside. When there is no outside signal, G-alpha joins the other two proteins. When they are together, these proteins are “off” (Figure 1A).

When the cell receives the signal, G-alpha-q separates from the other two proteins (Figure 1B). These proteins are now “on” and can turn on many different pathways. Proteins in pathways work together to do specific jobs within the cell. G-alpha proteins mainly turn on pathways that tell the cell to grow.



How are GNAQ mutations involved in melanoma?

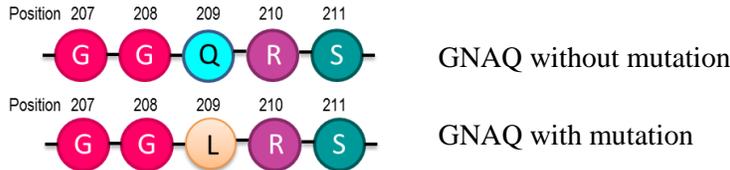
In healthy cells, when the signal is no longer needed, GNAQ turns itself off and joins the other two proteins. Some mutations in GNAQ do not allow it to turn off. This means it is always able to turn on some signaling pathways that help the cell grow. This may cause the cell to grow out of control, which can lead to cancer.

How common are GNAQ mutations in melanoma?

About half of melanomas that start in the eye (uveal melanoma) have a mutation that changes the GNAQ protein. These mutations are rare in melanomas in other parts of the body.

What is the GNAQ Q209L mutation?

GNAQ Q209L is a specific variation in the GNAQ protein¹. Proteins are long chains of amino acids². The GNAQ protein has 359 amino acids. GNAQ with no mutation³ at amino acid position 209 has a glutamine, or Q for short. The amino acid at position 209 in GNAQ with the Q209L mutation is a leucine, or L for short.



What is the effect of this mutation?

The Q209L mutation⁴ keeps GNAQ turned “on.” This can cause cells to grow out of control, which can lead to cancer (Figure 2).

Are there targeted therapies⁵ for GNAQ mutations?

There are no drugs that target GNAQ right now. But, you should talk to your doctor about your treatment options.

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

Your cancer cells might have mutations⁶ in this gene⁷ or in other genes that were not tested. Your genetic test⁸ results will still help your doctor determine the best treatment for you.

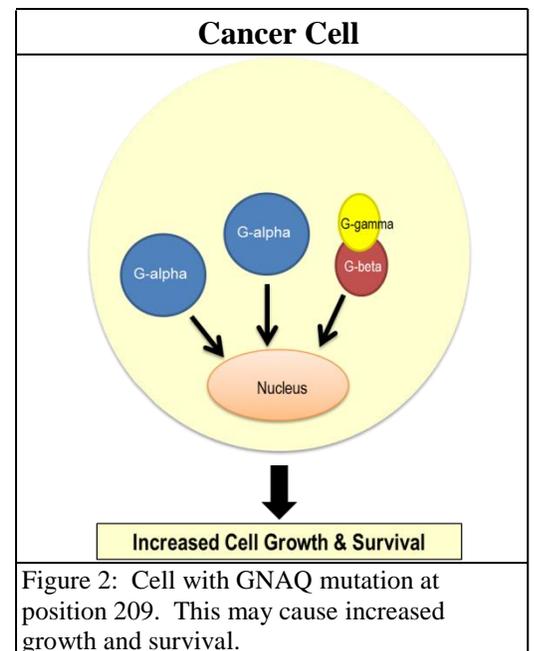


Figure 2: Cell with GNAQ mutation at position 209. This may cause increased growth and survival.