How Genetics and Family History Contribute to Melanoma Risk

Learn more about melanoma risk factors, hereditary melanoma, and genetic testing.

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If you have a family history of melanoma, you may be worried about how much genetics – traits passed down from biological parents to their children – contribute to your risk of developing melanoma, or other skin cancers. This article will outline genetic risk factors that can be inherited and cause an increased likelihood of developing melanoma.

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The Most Common Risk Factors for Developing Melanoma

We know that about 90% of melanomas are caused by UV exposure. This means that most cases of skin cancer, including melanoma, are attributed to lifestyle factors that result in exposure to ultraviolet (UV) radiation – and not genetic factors. These are considered sporadic cases, meaning it occurs in people who do not have a family history of melanoma or have an inherited mutation in their DNA that would increase their risk for melanoma.

For most families, even those with multiple members who have developed melanoma, it's their shared history of sun exposure, such as regular trips to the beach, that put them at increased risk. It is important to remember that getting 5 or more blistering sunburns between the ages of 15-20 can increase your risk of getting melanoma by 80%.

Hereditary Melanoma and Genetic Predispositions

Genetic changes in melanoma tumor cells cannot be passed down from parents to children. But a genetic change that increases the risk of developing melanoma or another cancer can be passed down, what doctors call an inherited trait. According to the National Cancer Institute, up to 10% of cancers – including melanomas – may be caused by inherited genetic changes. If you have one of these inherited genetic changes, you have a genetic predisposition that increases your risk of developing a cancer during your lifetime. It's important to note that not everyone with a genetic predisposition will actually develop cancer.

People who have a genetic predisposition for melanoma are often diagnosed with melanoma at a younger age. Those impacted regularly develop multiple primary melanomas over their lifetime. Among these people, a gene mutation – or a change in the DNA sequence of a gene, causes normal cells to develop abnormally or grow out of control, which may ultimately lead to melanoma. In families with a genetic predisposition to melanoma, their lifetime risk of getting melanoma could be as high as 60-90%, depending on the gene(s) that are mutated. Inherited mutations in the following genes are associated with a higher risk of developing melanoma, including:

- CDKN2A,
- CDK4,
- TERT,
- POT1,
- ACD,
- TERF2IP,
- MITF, and
- BAP1.

However, most of these gene mutations occur with a relatively low frequency, which suggests that most hereditary melanomas involve multiple genes that are mutated. While mutations in all of these genes are associated with an increased risk of developing melanoma, there are many differences among them including how common they are, how much they increase an individual's risk for developing melanoma, where the associated melanomas may occur on the body (i.e. limbs versus torso), or if they also lead to a higher risk of developing other cancers. Researchers are currently working to better understand these inherited gene mutations and how they contribute to an increased risk for melanoma and other cancers.

CDKN2A mutations are the most common mutated gene associated with an increased risk of developing melanoma, accounting for 22% of cases. In patients with a CDKN2A mutation, melanoma typically occurs earlier in their lifetime, around 33-45 years of age compared to 53-61 year of age in the general population.

Mutations in CDK4, TERT, POT1, ACD, TERF2IP, MITF, and BAP1 are all rarer than CDKN2A, but can predispose a patient to early onset melanoma and increase the risk of developing other cancers, such as non-melanoma skin cancers, breast cancer, pancreatic cancer, ovarian cancer, cervical cancer, and stomach cancer. Mutations in these genes may also be linked to certain characteristics that are associated with an increased susceptibility of developing skin cancers, such as red or blonde hair, freckles, blue or green eyes, and lighter skin tones that burn more easily.

Screening for Gene Mutations & Genetic Counseling

Genetic tests are available that can let you know if you have any genetic mutations associated with an increased risk of melanoma. Your doctor can help you understand if genetic counseling may be helpful.

According to the American Academy of Dermatology, good candidates for genetic counseling have one (or more) of the following:

- 3 or more melanomas that have grown deep into your skin (or spread), especially if one melanoma was diagnosed before your 45th birthday;
- 3 or more blood relatives on one side of your family who have had melanoma or cancer of the pancreas;
- 2 or more unusual-looking moles called Spitz nevi; and/or
- 1 or more Spitz nevi and a close blood relative has (or had) mesothelioma (a type of cancer), meningioma (a type of brain tumor), or melanoma of the eye.

Your doctor can refer you to a genetics counselor who can help you better understand your potential risks, benefits, and drawbacks of testing in your specific situation. They will also provide post-test counseling where they help you understand your results and what they mean for you and your family.

If you decide to go forward with genetic testing, you will need to provide a sample of your DNA to be analyzed for potential mutations. A blood draw or even swabbing the inside of your cheek or mouth can provide enough DNA for testing purposes.

While genetic testing can provide you with a lot of useful information, it is important to remember that it cannot tell you definitively if you will or will not develop melanoma. However, it can be a useful tool to help guide your behavior to reduce your risk of melanoma. In your discussions with a genetic counselor, you may also ask whether any of the genetic mutations that were found are associated with increased risk for other cancers and what you can do to follow-up. You should also consider sharing the results with close family members, so they can assess their own risk of developing melanoma.

Individuals with an increased genetic risk of developing melanoma should see a dermatologist for more frequent skin cancer screenings, such as a full body skin exam every 3-6 months, including thorough examinations of areas such as the scalp, oral cavity, or genital mucosa. Your doctor may also recommend additional screening including digital dermoscopy or total body photography. Frequent self-examination of your own skin is also important to catch any new or changing spots on your body to flag for your doctor. It is also critical to protect your skin from the sun every day

by using sunscreen and avoiding direct sun exposure as much as possible. These lifestyle changes are recommended for all melanoma patients and their relatives, regardless of whether they have a genetic risk, for the prevention and early detection of melanoma.

How to Get Involved in Melanoma Research

Dr. Pauline Funchain of the Cleveland Clinic believes that hereditary melanoma may be more common than most doctors currently suspect. To study this question, Dr. Funchain has established The Gross Family Melanoma Registry to explore the genetic risk factors of melanoma and other cancers. Participants include families with unusually high rates of cancer, who undergo genetic testing and additional follow-up tests over several years. The registry aims to discover important information on hereditary melanoma that will help doctors identify individuals with a higher risk who have not yet developed cancer, as well as patients with melanoma who might be at risk of developing other cancers.

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