The Genetics of Melanoma

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What are genes?

Genes carry information in the form of DNA within each cell of the human body. Researchers estimate that there are 30,000 different genes in each cell. Genes are packaged onto chromosomes. There are 23 pairs of chromosomes in each cell. One chromosome of each pair is inherited from the person's father and one from the person's mother.

Genes control how a cell functions, including how quickly it grows, how often it divides, and how long it lives. To control these functions, genes produce proteins that perform specific tasks and act as messengers for the cell. Therefore, it is essential that each gene have the correct instructions or "code" for making its protein so that the protein can perform the proper function for the cell.

What role do genes play in melanoma?

Many cancers begin when one or more genes in a cell are mutated (changed), creating an abnormal protein or no protein at all. The information provided by an abnormal protein is different from that of a normal protein, which can cause cells to multiply uncontrollably and become cancerous.

A person may either be born with a genetic mutation in all of their cells (germline mutation) or acquire a genetic mutation in a single cell during his or her lifetime. An acquired mutation is passed on to all cells that develop from that single cell (called a somatic mutation). Somatic mutations can sometimes be caused by environmental factors, such as cigarette smoke. Most melanomas (about 90%) are considered sporadic, meaning that the damage to the genes occurs by chance after a person is born, and there is no risk of passing on the gene to a person's children. An increased risk of melanoma occurs when specific gene mutations are passed within a family from generation to generation. Keep in mind that melanoma itself is not inherited; it is the increased risk of developing melanoma that is inherited. Many people who have an increased risk of melanoma never develop the disease; only 10% of melanoma is familial (runs in the family).

What are the chances a mutated gene is inherited?

Every cell usually has two copies of each gene: one inherited from a person's mother and one inherited from a person's father. Hereditary melanoma follows an autosomal dominant inheritance pattern, in which a mutation needs to happen in only one copy of the gene for the person to have an increased risk of getting the disease. This means that a parent with a gene mutation may pass on a copy of the normal gene or a copy of the gene with a mutation. Therefore, a child who has a parent with a mutation has a 50% chance of inheriting that mutation. A brother, sister, or parent of a person who has a gene mutation also has a 50% chance of having the same mutation.

What is a person's average risk for melanoma?

A person with an average risk of melanoma has about a 2% chance of developing melanoma during his or her lifetime.

How can a person know if he or she has inherited a genetic mutation that increases his or her risk of melanoma?

Only genetic testing [2] can determine whether a person has a genetic mutation. Genetic testing for melanoma risk is available on a limited basis. Doctors suggest that families with more than one person who has been diagnosed with melanoma consider participating in genetic research studies, so that more can be learned about how genetic mutations influence the melanoma risk. Even in families with several people who have melanoma, a changed gene is often not found.

How does a person know if melanoma runs in the family?

An inherited risk of melanoma is suspected if two or more first-degree relatives (parents, brothers, sisters, children) are diagnosed with melanoma. Inherited melanoma is sometimes called familial melanoma. For people living in the southern United States or other parts of the world where they are exposed to intense sunlight, familial melanoma is suspected if three or more first-degree relatives develop melanoma.

There are other important signs that suggest that melanoma may run in a family, including:

- More than one melanoma diagnosis in the same person
- Melanoma diagnosed in early adulthood. Inherited melanoma in American families often develops around 35. Most women develop melanoma before age 50.
- More than one atypical or dysplastic nevi, which are more common for people who have an increased risk of melanoma.

Most experts strongly recommend that people concerned about their family history of melanoma consult a genetic counselor [3]. Genetic counselors are trained to assess the potential for hereditary cancer risk in a family and can identify appropriate genetic testing or research studies.

What is a person's risk if melanoma runs in the family?

If a person has a first-degree relative with melanoma, his or her risk of developing melanoma is two to three times greater than the average risk. The risk is higher if several family members that live in different locations have been diagnosed with melanoma.

Which inherited genetic mutations raise the risk of melanoma?

There are several genes thought to be associated with an increased risk of melanoma. However, research to better understand how these genes affect the risk of melanoma is ongoing.

Familial malignant melanoma [4]. There are at least three different genes have been linked to hereditary melanoma. Families with mutations in these genes may have multiple dysplastic nevi (flat moles that are irregular in shape or color). Although dysplastic nevi are likely to be related to altered genes, the specific genes involved have not been identified. The association of familial melanoma and multiple dysplastic nevi is also sometimes called familial atypical multiple mole melanoma (FAMMM) or atypical nevus syndrome. Families with inherited melanoma may also have an increased risk of developing pancreatic cancer [5] and possibly other cancers.

Melanoma-astrocytoma syndrome. People with this rare condition have an increased risk of melanoma and astrocytoma [6] (a type of brain tumor). The specific gene for this condition is thought to be located on chromosome 9. Families with both melanoma and astrocytoma have been shown to have changes in a gene called *CDKN2A* gene, which affects tumor growth.

Are there other genetic conditions associated with an increased risk of melanoma?

Other genetic conditions that are associated with an increased risk of melanoma are described below.

Xeroderma pigmentosum [7]. Xeroderma pigmentosum (XP) is a group of rare conditions that makes a person's cells unable to repair DNA damage caused by ultraviolet (UV) light exposure, such as sunshine. Signs of XP are caused by the increased sensitivity to UV light, and include dry skin, abnormal pigmentation, severe freckling, and blistering after minimal sun exposure. People with this condition have a high risk of skin cancer [8], including melanoma (more than a thousand times more likely than the general population), and noncancerous skin abnormalities. People with XP also have an increased risk of other types of cancers including leukemia [9], brain tumors [10], stomach cancer [11], lung cancer [12], breast cancer [13], uterine cancer [14], and testicular cancer [15].

Retinoblastoma [16]. Retinoblastoma is a childhood eye tumor. Children with hereditary retinoblastoma have an increased risk of developing other cancers as they grow older, especially melanoma (50 times more likely than the general population). They also have a higher risk for osteosarcoma [17] (a type of bone cancer), other sarcomas [18], leukemia [19], lymphoma [20], melanoma, lung cancer [12], and bladder cancer [21].

Li-Fraumeni syndrome (LFS) [22]. LFS is a rare condition associated with a specific genetic mutation. People with LFS have a higher risk of developing osteosarcoma [17], soft tissue sarcoma [18], leukemia [23], breast cancer [13], brain cancer [10], and adrenal cortical tumors [24]. People with LFS have developed melanoma, but the risk of developing melanoma is not known.

Werner syndrome [25]. Werner syndrome is a rare condition that causes premature aging and an increased risk of cancer, specifically osteosarcoma [17], other sarcomas [18], melanoma, and thyroid cancer [26].

Hereditary breast and ovarian cancer (HBOC) syndrome [27]. HBOC is associated with mutations in the *BRCA1* and/or *BRCA2* (BRCA stands for BReast CAncer). Women with HBOC have an increased risk of breast cancer [28] and ovarian cancer [29]. Men with HBOC have an increased risk of breast cancer [13] and prostate cancer [30]. People with HBOC also have an increased risk of melanoma, specifically people who have a mutation on the *BRCA2* gene.

Cowden syndrome (CS) [31]. CS is a rare genetic condition caused by a specific genetic mutation. People with CS have an increased risk of developing breast cancer [28] and noncancerous breast changes and noncancerous and cancerous tumors of the thyroid cancer [26] and endometrium [14] (lining of the uterus). People with CS have developed melanoma; however, it is not known whether having CS increases a person's risk of developing melanoma.

What is your risk level?

In addition to family history, other environmental and lifestyle factors may increase your risk of melanoma. Discussing your family history and personal risk factors, especially the type and number of moles (such as dysplastic nevi), complexion, and extensive freckling with a doctor helps you

better understand your risk. People with risk factors for melanoma are encouraged to see their doctor at least once a year for skin examinations. The ABCDE (Asymmetry, Border, Color, Dimension, Evolution) criteria are most commonly used in the diagnosis of early melanoma. People with a higher than average risk may benefit from sun-protective behavior [32] and early detection strategies.

A risk factor [33] is anything that increases a person's risk of developing cancer. Having a particular genetic mutation linked to melanoma cannot predict that a person will develop cancer. Controllable risk factors also play a large role in the development of melanoma. Sun or other types of ultraviolet light exposure (such as tanning beds) are the most important controllable risk factors for melanoma. To prevent melanoma, it is recommended that people limit sun exposure, particularly at mid-day, seek shade when outdoors, wear protective clothing, and use sunscreens as directed. Tanning parlors and sun beds should not be used. Talk with a doctor for more information about melanoma risk factors, screening, and prevention.

More Information

Genetics [34]

Guide to Melanoma [35]

Sharing Genetic Test Results With Your Family [36]

Direct-to-Consumer Genetic Testing [37]

Links:
[1] http://www.cancer.net/about-us
[2] http://www.cancer.net/node/24895
[3] http://www.cancer.net/node/24907
[4] http://www.cancer.net/node/18853
[5] http://www.cancer.net/node/19495
[6] http://www.cancer.net/node/18488
[7] http://www.cancer.net/node/19727
[8] http://www.cancer.net/node/19618
[9] http://www.cancer.net/patient/Cancer+Types
[10] http://www.cancer.net/node/18562
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