MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Hereditary Melanoma

Cancer in general

Cancer is a common disease. It is expected that one in every three people in the U.S. will develop cancer over their lifetime. The vast majority of cancers are not primarily due to an inherited factor. Individuals can develop cancer due to "sporadic factors" such as chance events, environmental exposures or lifestyles. Mainly inherited factors (altered cancer susceptibility genes) are responsible for only a small number of cancer cases, approximately 5-10%.

There are several features that are seen in a family when there is an inherited alteration in a cancer susceptibility gene. These include:

1) Multiple family members affected with the same (such as melanoma) or other possibly related cancers (such as melanoma and pancreatic cancer)
2) Young ages of onset for the cancers (melanoma which occurs at a younger than average age)
3) Individuals in the family may have multiple cancers such as two separate, primary melanomas in the same person
4) Cancer occurring in multiple generations

Genetics

It is important to understand what "inherited" means. Inherited traits are passed from one generation of a family to the next. These traits, like eye color or hair texture, are passed on in the form of genes. Genes are located on structures called chromosomes. There are 46 chromosomes in every cell of our body, and they come in pairs. The chromosome pairs are numbered 1 through 22 and the 23rd pair is the sex chromosomes: XX for female; XY for male. One copy of each chromosome pair comes from our mother and the other from our father. Similarly, we pass on one copy of each chromosome pair to our children.

Each chromosome contains many hundreds of genes. Because we have two copies of each chromosome, we therefore have two copies of each gene. Each gene is made up of DNA, which is the information that codes for a particular trait or condition. The sequence of DNA is very specific and if there is an alteration (or change) in the DNA pattern in any gene, this may cause the gene to not function properly. Alterations in certain genes can lead to a higher susceptibility to specific disease. A gene that could lead to a higher susceptibility to cancer is called a cancer predisposition gene.

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Melanoma Genetics

There are undoubtedly multiple genes that can lead to a higher susceptibility to melanoma. One of these genes is called CDKN2A. CDKN2A is sometimes referred to as p16. It is important to realize that these two names (CDKN2A and p16) refer to the same (single) gene. This gene, which is located on the short arm of chromosome 9, controls growth and death of cells. Therefore, if this gene is altered, the cell can grow into a tumor. It is estimated that a person with a CDKN2A alteration has a greater than 50% chance of developing melanoma during their lifetime (one study estimates a 76% lifetime risk in the United States). There is also an increased risk of developing melanoma more than once and people with a CDKN2A alteration have a younger average age of diagnosis. It is also believed that *some* families with alterations in CDKN2A have an increased risk of pancreatic cancer too. What is important to realize is that only a small proportion of people with melanoma or family histories of melanoma have hereditary alterations in CDKN2A. However, the more features seen in the family (multiple people with melanoma, melanoma primary melanomas in one person, etc.), the more likely it is that a hereditary alteration in CDKN2A is present.

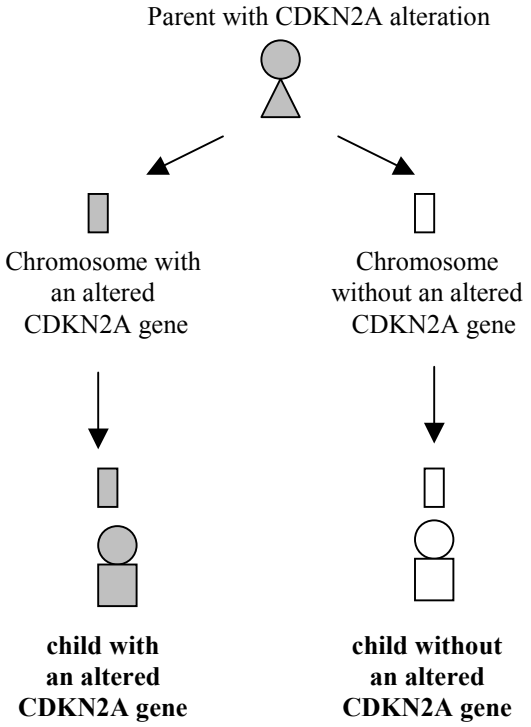
Inheritance of CDKN2A alterations

Familial melanoma is passed on in families in an inheritance pattern known as *autosomal dominant*. Autosomal means that the both men and women can have the condition and the genes are not located on the sex chromosomes. Dominant means that if a parent has a mutation, each child has a 1 in 2 or 50% chance of inheriting the chromosome with the mutation on it and, thus, would be at significant risk of developing cancer.

What is the chance that a person with an altered CDKN2A gene will pass it on to their children? Remember that each of us have two copies of every gene. If a person is identified as having an altered CDKN2A gene, we would assume that the other copy of the gene is working because it is extremely unlikely that an individual is born with both copies of a gene altered. Remember also that we pass on only one copy of each gene to each of our children. There is a 50% or 1 in 2 chance that each child would inherit an altered gene and a 50% chance that each of them would inherit a working gene.

See Figure 1 below.

Figure 1: Inheritance



Conclusion: 1 in 2 or 50% chance for each child to inherit an altered gene

Genetic testing

It is possible to test someone's CDKN2A gene for inherited alterations. Genetic testing is done by taking a blood sample and checking the DNA pattern of a gene to look for an alteration in the gene (i.e. proofreading the gene). Results of genetic testing are most informative if a person who has been diagnosed with cancer is tested first. If an altered gene is identified in that person, the individual's blood relatives can be tested easily and the results are informative. That is, if the relative had the altered gene known to cause the cancer in the family, he/she would have an increased risk of developing cancer. If the relative did not inherit this altered gene, his/her risk of developing cancer would be the same as an individual in the general population.

There are many issues to consider before having genetic testing for alterations in CDKN2A. First, most families with melanoma are already being screened appropriately for skin cancer and are following recommendations for avoidance of sun exposure. Genetic testing *may no*t change screening recommendations for anyone in the family currently following these recommendations – everyone in the family will need to continue to undergo routine dermatological exams regardless of their genetic test results although the frequency/intensity of exams may change.

It is uncertain whether individuals having genetic testing for CDKN2A will find this information useful. For this reason, genetic testing for alterations in the CDKN2A gene has not been routinely recommended by all healthcare providers. Having genetic testing is a personal choice.

Genetic information can have many emotional consequences for the person being tested. Individuals may feel anxiety and/or depression as they await their result, and may experience many different emotions once they receive their result. In addition, this information can have widespread implications for other family members, and it may be difficult to inform relatives if an alteration is identified.

The threat of genetic discrimination is of concern for some individuals. Genetic discrimination is the use of genetic information (e.g. CDKN2A test results) by health insurers, employers, life insurers and disability insurers. There are no documented cases of individuals suffering from genetic discrimination due to hereditary cancer syndrome genetic testing in terms of their health insurance at this point. In addition, it is *illegal* in the state of Massachusetts to discriminate based on genetic information in health insurance and employment. Life insurance is not protected by this law. It is legal for a life insurance company to adjust your premiums and/or choose not to insure you if they found out about this type of information.

Testing logistics

It is essential that genetic testing for CDKN2A alterations, if considered, occur with appropriate genetic counseling and education. At MGH, testing for CDKN2A alterations involves two visits with a genetic counselor and physician team at the MGH: a pre-test education session and a result disclosure session. There is no cost for the genetic counseling visits, but the cost of the lab test is the responsibility of the person being tested (unless you participate in a study which covers the cost of the test). The laboratory charges a fee of around $745 for full gene testing. In many cases, this fee is covered (in full or in part) by insurance. We are happy to assist in looking into insurance issues but we cannot guarantee coverage.

Recommendations for those at risk of melanoma

It is important that everyone with a family history of melanoma be screened appropriately. This means:

1) Avoid sun exposure, wear sun-protective clothing including hats, and use sunscreen with UVA and UVB protection
2) Monitor all skin changes very carefully and regularly looking for changes in size, color and shape of moles - have someone check in areas not visible to you
3) Have a qualified dermatologist examine your skin every 6 months and come in earlier for examination if you note any suspicious changes
4) Have any suspicious-looking marks removed and examined (biopsied)

If you are interested in pursuing genetic testing or have further questions regarding testing, please call the Massachusetts General Hospital Melanoma Genetics Program at 617-724-1971.