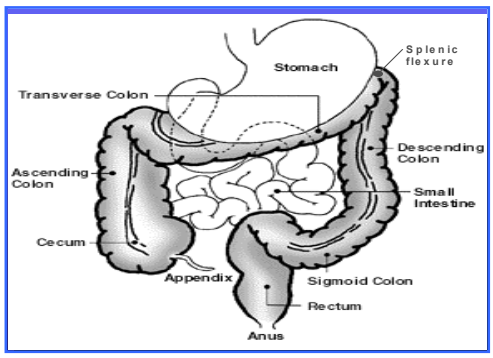
# Hereditary Nonpolyposis Colorectal Cancer (HNPCC) and the MSH6 Gene

## What is Hereditary Nonpolyposis Colorectal Cancer (HNPCC)?

***Hereditary nonpolyposis colorectal cancer is an inherited cancer syndrome caused by an altered gene that is passed on in a family.***




HNPCC is a dominant condition, meaning that people with HNPCC have a 50% chance of passing the HNPCC gene mutation (change) to each of their children. With HNPCC, the lifetime risk for colorectal cancer (CRC) is approximately 80% and the lifetime risk of endometrial cancer is 40%. The lifetime risk associated with the other cancers (small intestine, urinary tract, stomach, ovaries, and bile duct) is 10% or less.

Mutations or large deletions in 5 different genes (MLH1, MSH2, MSH6, PMS2, and PMS1) have been found to cause HNPCC. Most of the mutations have been detected in the MLH1 and MSH2 genes. Usually, they are point mutations, meaning that a single DNA base (letter) is altered. However, it is now believed that 20-30% of changes in the MSH2 gene, in particular, are due to large deletions of genetic material that were not detectable using previous testing methods. Individuals with a mutation or large deletion in any one of these 5 genes have a much higher risk for developing colorectal cancer and other cancers described above. These genes, which are known to be involved with HNPCC, are mismatch repair genes. A mismatch repair gene corrects mistakes that occur in DNA. DNA is what tells our bodies how to grow and develop. If there is a mistake in the DNA, which cannot be corrected by one of these mismatch repair genes, the DNA becomes unstable. When the DNA is unstable, it is termed “microsatellite instability” (MSI). This unstable DNA is a key feature of cancers associated with HNPCC. An HNPCC tumor is usually MSI-High, which means it shows a large amount of instability in the DNA, or the tumor is MSI-Low, which means it only shows a small amount of instability in the DNA.

## What is the MSH6 gene?

***The MSH6 gene is one of the genes known to cause HNPCC.***

The first report of human MSH6 mutations was in 1997 by Akiyama et al. An article in the American Journal of Human Genetics in 2002 (Berends, et al.) describes the clinical and molecular characteristics of individuals with a mutation in the MSH6 gene. This article describes 25 patients and 8 relatives of these patients, all of whom had a mutation in the MSH6 gene. Five mutations in the MSH6 gene were found in 12 of the patients. These five mutations are known to hinder the gene from repairing mistakes in the DNA, thereby increasing the individual’s risk for developing cancer.

## Look for These Clues

***Family history is an important risk factor for hereditary colorectal cancer.***

When reviewing your family history, it is important to consider both your father’s and your mother’s side of the family since an altered gene can be inherited from either parent. Gather information on all types of cancer because other cancers can occur as part of hereditary nonpolyposis colorectal cancer. Certain “red flags” may suggest a higher risk for hereditary nonpolyposis colorectal cancer. These include:

- The diagnosis of colon or rectal cancer before age 50
- The presence of several family members with colorectal cancer
- Having several family members with colon polyps
- Family members with ovarian, endometrial, stomach, ureter, biliary, or small intestine cancers

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## Who should be tested for mutations in the MSH6 gene?

***A recent article described characteristics associated with individuals carrying a MSH6 mutation.***

If you or your family members show any of the following characteristics described by Berends et al., you may want to talk with a genetic counselor about MSH6 gene testing:

1. Most of the mutations in the MSH6 gene have been found in families that **may** have an HNPCC diagnosis, but the family does not meet all of the clinical criteria to be given the HNPCC diagnosis.

2. A key feature of patients who carry a mutation in the MSH6 gene is a low level of instability in their tumors (MSI-Low). This is different from individuals with mutations in the MLH1 or MSH2 genes who mostly have a high level of instability in their tumors (MSI-High).

3. Colorectal cancer and endometrial cancer are diagnosed at an older age in individuals with a mutation in the MSH6 gene compared to individuals with mutations in the MLH1 or MSH2 gene.

4. There are more cases of endometrial cancer in individuals with a mutation in the MSH6 gene than in individuals with a mutation in the MLH1 or MSH2 gene.

5. Most individuals with a mutation in the MSH6 gene have colorectal cancers which are located on the left side of the colon; this includes the descending colon, the sigmoid colon and the rectum. However, it is important to note that many people with HNPCC have tumors on the right side of the colon.

## What does this mean for me?

***Talk with your health care provider to determine if genetic testing is right for you and your family.***

MSH6 genetic testing may be useful if you or your family fit any of the descriptions below:

- Your family history looks like HNPCC;
- You have already received inconclusive MLH1 and MSH2 test results;
- You or your family has a “low” or “negative” microsatellite instability test result.

Genetic testing and genetic counseling for HNPCC is currently available. Genetic counselors interpret information about genetic diseases or disorders, analyze inheritance patterns and risks of occurrence, identify high-risk family members, and review available options for prevention, screening, genetic testing, and treatment. If you are interested in talking about your family history and the new genetic testing options available, please contact Linda Thompson at (410) 502-7082 to set up an appointment.

## References


Akiyama Y, Sato H, Yamada T, Nagasaki H, Tsuchiya A, Abe R, Yuasa Y (1997) Germ-line mutation of the *hMSH6/GTBP* gene in an atypical hereditary nonpolyposis colorectal cancer kindred. Cancer Research 57:3920-3923.

Berends M, Wu Y, Sijmons R, Mensink R, Sluis T, Hordijk-Hos J, Vries E, Hollema H, Karrenbeld A, Buys C, Zee A, Hofstra R, Kleibeuker J (2002) Molecular and Clinical Characteristics of *MSH6* Variants: An Analysis of 25 Index Carriers of a Germline Variant. American Journal of Human Genetics 70:26-37.



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