Cancer Genetics Summary

Hereditary Non-Polyposis Colorectal Cancer

Hereditary Non-Polyposis Colorectal Cancer (HNPCC), also known as Lynch syndrome, represents about 5 percent of all colorectal cancers.

HNPCC tends to occur at an earlier age (about age 45) than other colorectal cancers, is usually located on the right side of the colon and can occur in more than one area and at multiple times. Mutations in at least six different genes have been associated with the HNPCC syndrome and result in a predisposition for colon and rectal cancer and for certain other cancers that occur outside the colon, called extracolonic cancers. The extracolonic cancers involve the lining of the uterus or womb (endometrium), stomach, small intestine, gallbladder and associated structures such as the bile duct, ovary, pancreas and the pelvis of the kidney or the ureter. We also see an increased risk for brain and sebaceous cell carcinoma with specific mutations in the mismatch repair genes (MMR), which will result in a variance of HNPCC.

HNPCC can be suspected if the “Amsterdam Criteria” are present:

- Three or more relatives have had colorectal cancer, including at least one first-degree relationship (parent, child or sibling).
- Two successive generations are affected.
- At least one colorectal cancer occurred before age 50.
- It has been established that there is not a history of Familial Adenomatous Polyposis Syndrome (FAP).

Another set of criteria, called the “Bethesda Criteria,” is used to decide when to perform a laboratory evaluation called MSI (microsatellite instability). A family that does not specifically fit these criteria is considered “suspected HNPCC.” Sometimes HNPCC is referred to as Lynch syndrome 1 (families with colon cancers only) and Lynch syndrome 2 (families with both colon and extracolonic cancers).

HNPCC Cancer Risks

Colon cancer is the most common cancer in males who carry an altered HNPCC predisposing gene. A recent HNPCC study suggests there is a 90 percent risk for males and a 30 percent risk for females of developing colon cancer by age 80. An individual with HNPCC who has had one colon cancer has a 30 percent risk for developing another colon cancer within 10 years and a 50 percent chance within 15 years.

Endometrial cancer may be the most common cancer in women with HNPCC and seems to occur earlier than in the general population. Women with HNPCC have a 30 percent risk of developing endometrial cancer by age 70, with a 40-50 percent lifetime risk. This is compared to 3 percent lifetime

risk in the general population.

Increased risks of other types of cancer associated with HNPCC include:

- Stomach (19 percent)
- Ovaries (18 percent)
- Gallbladder and associated structures (18 percent)
- Pancreas (10 percent)
- Transitional cell carcinoma of the kidney pelvis or ureter (10 percent).

HNPCC Genes

The mismatch repair (MMR) genes that are known to cause HNPCC when altered by cancer-predisposing gene mutations are called MLH1, MSH2, MSH6 and PMS2. When working properly, these genes are responsible for certain types of DNA sequence repairs. When any one of these genes is mutated in a harmful way, DNA repair might not occur properly and mistakes in many different genes can begin to accumulate. The accumulation of genetic mistakes in a cell can cause the cell to become cancerous. The other gene known to have mutations that predispose to HNPCC in a few families is one of the genes normally repaired by the MMR genes.

Genetic Testing for HNPCC

When the mismatch repair genes are not working properly, differences in small regions of DNA sequences called microsatellites can be detected in HNPCC-associated cancer tissue. If available, tumor tissue testing of colon or endometrial cancer is recommended prior to initiating MMR gene mutation testing. If a tumor screening test shows “microsatellite instability,” it is more likely that the cancers were caused by an HNPCC gene alteration. However, as not all HNPCC tumors show instability, that does not guarantee that an altered HNPCC-predisposing gene is not present. Another option is Immunohistochemistry (IHC) staining, which can identify the absence of a protein in a tumor. If a protein is absent it may indicate a problem with the gene that makes that protein.

Most laboratories that offer MMR gene mutation testing only sequence or test for the MLH1, MSH2, and MSH6 genes, as they are responsible for 65 percent of the cases of HNPCC. If an individual does not have a detectable mutation in these two genes, an HNPCC predisposition may still be present because:

- The HNPCC gene causing the cancer predisposition was not tested.
- A gene change is present in MLH1, MSH2, or MSH6 that current testing methods are unable to detect.
- The predisposition is due to an as yet undiscovered cancer susceptibility gene.

Predisposition gene testing is best performed on someone who has had cancer. If that individual is found to have a change in the suspect gene, then other relatives can reliably be tested. If the underlying cause of cancer in your family is found to be due to an HNPCC-associated gene and your test results show you have the mutation, it means you have an increased lifetime risk for cancer. It will not,

however, predict if or when a cancer will occur or which organ or organs (e.g., colon, uterus, etc.) will be affected.

If your test results indicate that you did not inherit the predisposing gene mutation, your chance of developing cancer over a lifetime would be the same as the general population. If you do not have the altered predisposing gene known to be present in your family, you cannot pass the mutation on to your children and their risk would also be the same as the general population.

For more information or questions, call 503-413-6534.

Prepared by Paul Dorsey, cancer genetic counselor, Legacy Cancer Institute.

1/30/12