MLH1 gene

mutL homolog 1

Normal Function

The *MLH1* gene provides instructions for making a protein that plays an essential role in repairing DNA. This protein helps fix errors that are made when DNA is copied (DNA replication) in preparation for cell division. The MLH1 protein joins with another protein called PMS2 (produced from the *PMS2* gene), to form a two-protein complex called a dimer. This complex coordinates the activities of other proteins that repair errors made during DNA replication. The repairs are made by removing a section of DNA that contains errors and replacing the section with a corrected DNA sequence. The *MLH1* gene is one of a set of genes known as the mismatch repair (MMR) genes. The MLH1 protein can also form a dimer with the MLH3 or PMS1 protein (each produced from different genes), but the function of these dimers is not well understood.

Health Conditions Related to Genetic Changes

Constitutional mismatch repair deficiency syndrome

About 10 variants (also known as mutations) in the *MLH1* gene have been associated with condition called constitutional mismatch repair deficiency (CMMRD) syndrome. Individuals with this condition are at increased risk of developing cancers of the colon (large intestine) and rectum (collectively referred to as colorectal cancer), brain, and blood (leukemia or lymphoma). These cancers usually first occur in childhood, with the vast majority of cancers in CMMRD syndrome diagnosed in people under the age of 18. Many people with CMMRD syndrome also develop changes in skin coloring (pigmentation), similar to those that occur in a condition called neurofibromatosis type 1.

Individuals with CMMRD syndrome inherit two *MLH1* gene variants, one from each parent, while people with Lynch syndrome (described below) have a variant in one copy of the *MLH1* gene.

MLH1 gene variants result in near or complete loss of MLH1 protein production. A shortage of this protein eliminates mismatch repair activity and prevents the proper repair of DNA replication errors. These errors accumulate as the abnormal cells continue to divide. The errors disrupt other genes involved in important cellular processes, such as controlling cell growth and division (proliferation). If cell growth is uncontrolled, it can lead to childhood cancer in people with CMMRD syndrome.

It is thought that the features of neurofibromatosis type 1 in people with CMMRD syndrome are due to genetic changes in the *NF1* gene that result from loss of mismatch repair. These changes are present only in certain cells (somatic variants), whereas *NF1* gene variants that are present in all cells of the body cause neurofibromatosis type 1.

Lynch syndrome

About 40 percent of all cases of Lynch syndrome with an identified gene alteration are associated with inherited variants in the *MLH1* gene. Several hundred *MLH1* gene variants have been found in people with this condition. Lynch syndrome increases the risk of many types of cancer, particularly colorectal cancer. People with Lynch syndrome also have an increased risk of cancers of the endometrium (lining of the uterus), ovaries, stomach, small intestine, gallbladder ducts, upper urinary tract, and brain. By age 75, the risk of developing one of these cancers is 80 percent for women and 70 percent for men with an *MLH1* gene variant.

MLH1 gene variants involved in this condition prevent the production of the MLH1 protein from one copy of the gene or lead to an altered version of this protein that does not function properly. A decrease in functional MLH1 protein leads to an increase in unrepaired DNA errors during cell division. The errors accumulate as the cells continue to divide, which may cause the cells to function abnormally, increasing the risk of tumor formation in the colon or another part of the body.

Because there is some functional MLH1 protein produced from the normal copy of the gene, mismatch repair activity in Lynch syndrome is reduced but not absent, as it is in CMMRD syndrome (described above). This difference in DNA repair activity levels likely explains why cancers in Lynch syndrome generally develop in adulthood while those in CMMRD syndrome often affect children.

Some variants in the *MLH1* gene cause a form of Lynch syndrome called Muir-Torre syndrome. In addition to colorectal cancer, people with this condition have an increased risk of developing several uncommon skin tumors. These rare skin tumors include sebaceous adenomas and carcinomas, which occur in glands that produce an oily substance called sebum (sebaceous glands). Multiple rapidly growing tumors called keratoacanthomas may also occur, usually on sun-exposed areas of skin.

Ovarian cancer

Inherited changes in the *MLH1* gene increase the risk of developing ovarian cancer, as well as other types of cancer, as part of Lynch syndrome (described above). Women with Lynch syndrome have an 8 to 10 percent chance of developing ovarian cancer, as compared with 1.6 percent in the general population.

Other Names for This Gene

- hMLH1
- MLH1_HUMAN
- mutL (E. coli) homolog 1 (colon cancer, nonpolyposis type 2)

- mutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli)
- MutL protein homolog 1

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of MLH1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=4292[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28MLH1%5BTI%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- DNA MISMATCH REPAIR PROTEIN MLH1; MLH1 (https://omim.org/entry/120436)
- MUIR-TORRE SYNDROME; MRTES (https://omim.org/entry/158320)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/4292)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=MLH1[gene])

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Genomic Location

The *MLH1* gene is found on chromosome 3 (https://medlineplus.gov/genetics/chromosome/3/).

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