MSH6 gene

mutS homolog 6

Normal Function

The *MSH6* 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 MSH6 protein joins with another protein called MSH2 (produced from the *MSH2* gene) to form a two-protein complex called a dimer. This complex identifies locations on the DNA where errors have been made during DNA replication. Additional proteins, including another dimer called the MLH1-PMS2 dimer, then repair the errors by removing the mismatched DNA and replicating a new segment. The *MSH6* gene is a member of a set of genes known as the mismatch repair (MMR) genes.

Health Conditions Related to Genetic Changes

Constitutional mismatch repair deficiency syndrome

More than 15 variants (also known as mutations) in the *MSH6* gene have been associated with a 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 *MSH6* gene variants, one from each parent, while people with Lynch syndrome (described below) have a variant in one copy of the *MSH6* gene.

MSH6 gene variants result in near or complete loss of MSH6 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

Variants in the *MSH6* gene have been reported in about 13 percent of families with Lynch syndrome that have an identified gene variant. 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 60 percent for women and 40 percent for men with an *MSH6* gene variant. Endometrial cancer is especially common in women with Lynch syndrome caused by *MSH6* gene variants.

MSH6 gene variants involved in this condition lead to the production of an abnormally short, nonfunctional MSH6 protein; a partially active version of the protein; or no protein product from one copy of the gene. A decrease in functional MSH6 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 MSH6 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.

In a small number of people, variants in the *MSH6* 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

MedlinePlus Genetics provides information about Ovarian cancer

Other Names for This Gene

- G-T binding protein
- G/T mismatch-binding protein
- GTBP
- mutS (E. coli) homolog 6

- mutS homolog 6 (E. coli)
- MutS-alpha 160 kDa subunit

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of MSH6 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=2956[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28MSH6%5BTIAB%5D%29+OR+%28mutS+homolog+6%5BTIAB%5D%29%29+AND+%28g-t+mismatch-binding+protein%5BNM%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

- MUIR-TORRE SYNDROME; MRTES (https://omim.org/entry/158320)
- NEUROFIBROMATOSIS, TYPE I; NF1 (https://omim.org/entry/162200)
- MutS HOMOLOG 6; MSH6 (https://omim.org/entry/600678)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/2956)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=MSH6[gene])

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Genomic Location

The *MSH6* gene is found on chromosome 2 (https://medlineplus.gov/genetics/chromosome/2/).

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