

MLH1 Gene

Subjects: **Genetics & Heredity**

Contributor: Lily Guo

mutL homolog 1

genes

1. Introduction

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.

2. Health Conditions Related to Genetic Changes

2.1. Constitutional mismatch repair deficiency syndrome

About 10 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 mutations, one from each parent, while people with Lynch syndrome (described below) have a mutation in one copy of the *MLH1* gene.

MLH1 gene mutations 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 mutations), whereas *NF1* gene mutations that are present in all cells of the body cause neurofibromatosis type 1.

2.2. Lynch syndrome

About 40 percent of all cases of Lynch syndrome with an identified gene mutation are associated with inherited mutations in the *MLH1* gene. Several hundred *MLH1* gene mutations 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 mutation.

MLH1 gene mutations 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 mutations in the *MLH1* gene cause a variant 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.

2.3. 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.

3. 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

References

1. Andersen SD, Liberti SE, Lützen A, Drost M, Bernstein I, Nilbert M, Dominguez M, Nyström M, Hansen TV, Christoffersen JW, Jäger AC, de Wind N, Nielsen FC, Tørring PM, Rasmussen LJ. Functional characterization of MLH1 missense variants identified in Lynch syndrome patients. *Hum Mutat.* 2012 Dec;33(12):1647-55. doi:10.1002/humu.22153.
2. Bandipalliam P. Syndrome of early onset colon cancers, hematologic malignancies & features of neurofibromatosis in HNPCC families with homozygous mismatch repair gene mutations. *Fam Cancer.* 2005;4(4):323-33. Review.
3. Dominguez-Valentin M, Sampson JR, Seppälä TT, Ten Broeke SW, Plazzer JP, Nakken S, Engel C, Aretz S, Jenkins MA, Sunde L, Bernstein I, Capella G, Balaguer F, Thomas H, Evans DG, Burn J, Greenblatt M, Hovig E, de Vos Tot Nederveen Cappel WH, Sijmons RH, Bertario L, Tibiletti MG, Cavestro GM, Lindblom A, Della Valle A, Lopez-Köstner F, Gluck N, Katz LH, Heinimann K, Vaccaro CA, Büttner R, Görgens H, Holinski-Feder E, Morak M, Holzapfel S, Hüneburg R, Knebel Doeberitz MV, Loeffler M, Rahner N, Schackert HK, Steinke-Lange V, Schmiegel W, Vangala D, Pylvänäinen K, Renkonen-Sinisalo L, Hopper JL, Win AK, Haile RW, Lindor NM, Gallinger S, LeMarchand L, Newcomb PA, Figueiredo JC, Thibodeau SN, Wadt K, Therkildsen C, Okkels H, Ketabi Z, Moreira L, Sánchez A, Serra-Burriel M, Pineda M, Navarro M, Blanco I, Green K, Lalloo F, Crosbie EJ, Hill J, Denton OG, Frayling IM, Rødland EA, Vasen H, Mints M, Neffa F, Esperon P, Alvarez K, Kariv R, Rosner G, Pinero TA, Gonzalez ML, Kalfayan P, Tjandra D, Winship IM, Macrae F, Möslin G, Mecklin JP, Nielsen M, Møller P. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. *Genet Med.* 2020 Jan;22(1):15-25. doi:10.1038/s41436-019-0596-9. Sep;22(9):1569.
4. Dowty JG, Win AK, Buchanan DD, Lindor NM, Macrae FA, Clendenning M, Antill YC, Thibodeau SN, Casey G, Gallinger S, Marchand LL, Newcomb PA, Haile RW, Young GP, James PA, Giles GG, Gunawardena SR, Leggett BA, Gattas M, Boussioutas A, Ahnen DJ, Baron JA, Parry S,

- Goldblatt J, Young JP, Hopper JL, Jenkins MA. Cancer risks for MLH1 and MSH2 mutation carriers. *Hum Mutat*. 2013 Mar;34(3):490-7. doi:10.1002/humu.22262.
5. Kohlmann W, Gruber SB. Lynch Syndrome. 2004 Feb 5 [updated 2018 Apr 12]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from <http://www.ncbi.nlm.nih.gov/books/NBK1211/>
 6. Leclerc J, Flament C, Lovecchio T, Delattre L, Ait Yahya E, Baert-Desurmont S, Burnichon N, Bronner M, Cabaret O, Lejeune S, Guimbaud R, Morin G, Mauillon J, Jonveaux P, Laurent-Puig P, Frébourg T, Porchet N, Buisine MP. Diversity of genetic events associated with MLH1 promoter methylation in Lynch syndrome families with heritable constitutional epimutation. *Genet Med*. 2018 Dec;20(12):1589-1599. doi: 10.1038/gim.2018.47.
 7. Mitchell RJ, Farrington SM, Dunlop MG, Campbell H. Mismatch repair genes hMLH1 and hMSH2 and colorectal cancer: a HuGE review. *Am J Epidemiol*. 2002 Nov 15;156(10):885-902. Review.
 8. Morak M, Ibsler A, Keller G, Jessen E, Laner A, Gonzales-Fassrainer D, Locher M, Massdorf T, Nissen AM, Benet-Pagès A, Holinski-Feder E. Comprehensive analysis of the MLH1 promoter region in 480 patients with colorectal cancer and 1150 controls reveals new variants including one with a heritable constitutional MLH1 epimutation. *J Med Genet*. 2018 Apr;55(4):240-248. doi:10.1136/jmedgenet-2017-104744.
 9. Moufid FZ, Bouguenouch L, El Bouchikhi I, Chbani L, Iraqui Houssaini M, Sekal M, Belhassan K, Bennani B, Ouldim K. The First Molecular Screening of MLH1 and MSH2 Genes in Moroccan Colorectal Cancer Patients Shows a Relatively High Mutational Prevalence. *Genet Test Mol Biomarkers*. 2018 Aug;22(8):492-497. doi:10.1089/gtmb.2018.0067.
 10. Pande M, Wei C, Chen J, Amos CI, Lynch PM, Lu KH, Lucio LA, Boyd-Rogers SG, Bannon SA, Mork ME, Frazier ML. Cancer spectrum in DNA mismatch repair gene mutation carriers: results from a hospital based Lynch syndrome registry. *Fam Cancer*. 2012 Sep;11(3):441-7. doi: 10.1007/s10689-012-9534-6.
 11. Peltomäki P. Lynch syndrome genes. *Fam Cancer*. 2005;4(3):227-32. Review.
 12. Pennington KP, Swisher EM. Hereditary ovarian cancer: beyond the usual suspects. *Gynecol Oncol*. 2012 Feb;124(2):347-53. doi:10.1016/j.ygyno.2011.12.415. Review.
 13. Raevaara TE, Korhonen MK, Lohi H, Hampel H, Lynch E, Lönnqvist KE, Holinski-Feder E, Sutter C, McKinnon W, Duraisamy S, Gerdes AM, Peltomäki P, Kohonen-Corish M, Mangold E, Macrae F, Greenblatt M, de la Chapelle A, Nyström M. Functional significance and clinical phenotype of nontruncating mismatch repair variants of MLH1. *Gastroenterology*. 2005 Aug;129(2):537-49.
 14. South CD, Hampel H, Comeras I, Westman JA, Frankel WL, de la Chapelle A. The frequency of Muir-Torre syndrome among Lynch syndrome families. *J Natl Cancer Inst*. 2008 Feb

20;100(4):277-81. doi: 10.1093/jnci/djm291.

15. Tamura K, Kaneda M, Futagawa M, Takeshita M, Kim S, Nakama M, Kawashita N, Tatsumi-Miyajima J. Correction to: Genetic and genomic basis of the mismatch repair system involved in Lynch syndrome. *Int J Clin Oncol*. 2019 Sep;24(9):1012. doi: 10.1007/s10147-019-01515-w.

Retrieved from <https://encyclopedia.pub/entry/history/show/12637>