PMS2 gene

PMS1 homolog 2, mismatch repair system component

Normal Function

The *PMS2* 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 PMS2 protein joins with another protein called MLH1 (produced from the *MLH1* 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. Repairs are made by removing the section of DNA that contains errors and replacing it with a corrected DNA sequence. The *PMS2* 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 55 variants (also known as mutations) in the *PMS2* gene have been associated with a condition called constitutional mismatch repair deficiency (CMMRD) syndrome. *PMS2* gene variants are the most frequent cause of this condition. Individuals with CMMRD syndrome 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 *PMS2* gene variants, one from each parent, while people with Lynch syndrome (described below) have a variant in one copy of the *PMS2* gene.

PMS2 gene variants result in near or complete loss of PMS2 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 *PMS2* gene have been reported in about 6 percent of families with Lynch syndrome that have an identified gene alteration. 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, liver, gallbladder ducts, upper urinary tract, and brain. By age 75, the risk of developing one of these cancers is 30 percent for women and 25 percent for men with a *PMS2* gene variant. These variants lead to a form of Lynch syndrome with a lower risk of cancer development compared to other causes of this condition. Additionally, in people with a *PMS2* gene variant, cancer tends to occur at a later age compared to others with Lynch syndrome. The reason for this lower cancer risk is unclear.

PMS2 gene variants involved in this condition lead to the production of an abnormally short or inactive PMS2 protein from one copy of the gene. The altered protein cannot efficiently repair errors made during DNA replication. The errors accumulate as the cells continue to divide, increasing the risk of tumor formation in the colon or another part of the body.

Because there is some functional PMS2 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.

Alopecia areata

MedlinePlus Genetics provides information about Alopecia areata

Ovarian cancer

MedlinePlus Genetics provides information about Ovarian cancer

Other Names for This Gene

- PMS2 postmeiotic segregation increased 2 (S. cerevisiae)
- PMS2_HUMAN
- postmeiotic segregation increased (S. cerevisiae) 2

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of PMS2 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5395[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28PMS2%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- PMS1 HOMOLOG 2, MISMATCH REPAIR SYSTEM COMPONENT; PMS2 (https://omim.org/entry/600259)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/5395)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=PMS2[gene])

References

- Bandipalliam P. Syndrome of early onset colon cancers, hematologicmalignancies & features of neurofibromatosis in HNPCC families withhomozygous mismatch repair gene mutations. Fam Cancer. 2005;4(4):323-33. doi:10.1007/s10689-005-8351-6. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16341812)
- Dominguez-Valentin M, Sampson JR, Seppala TT, Ten Broeke SW, Plazzer JP, Nakken S, Engel C, Aretz S, Jenkins MA, Sunde L, Bernstein I, Capella G, BalaguerF, Thomas H, Evans DG, Burn J, Greenblatt M, Hovig E, de Vos Tot Nederveen CappelWH, Sijmons RH, Bertario L, Tibiletti MG, Cavestro GM, Lindblom A, Della Valle A,Lopez-Kostner F, Gluck N, Katz LH, Heinimann K, Vaccaro CA, Buttner R, Gorgens H,Holinski-Feder E, Morak M, Holzapfel S, Huneburg R, Knebel Doeberitz MV, LoefflerM, Rahner N, Schackert HK, Steinke-Lange V, Schmiegel W, Vangala D, PylvanainenK, 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, Sanchez A, Serra-Burriel M, Pineda M, Navarro M,Blanco I, Green K, Lalloo F, Crosbie EJ, Hill J, Denton OG, Frayling IM, RodlandEA, Vasen H, Mints M, Neffa F, Esperon P, Alvarez K, Kariv R, Rosner G, PineroTA, Gonzalez ML, Kalfayan P, Tjandra D, Winship IM, Macrae F, Moslein G, MecklinJP, Nielsen M, Moller P. Cancer risks by gene, age, and gender in 6350 carriersof pathogenic mismatch repair variants: findings from the Prospective LynchSyndrome Database. Genet Med. 2020 Jan;22(1):15-25. doi:10.

1038/s41436-019-0596-9. Epub 2019 Jul 24. Erratum In: Genet Med. 2020Sep;22(9): 1569. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/31337882)

- Gill S, Lindor NM, Burgart LJ, Smalley R, Leontovich O, French AJ, GoldbergRM, Sargent DJ, Jass JR, Hopper JL, Jenkins MA, Young J, Barker MA, Walsh MD, Ruszkiewicz AR, Thibodeau SN. Isolated loss of PMS2 expression in colorectalcancers: frequency, patient age, and familial aggregation. Clin Cancer Res. 2005Sep 15;11(18):6466-71. doi: 10.1158/1078-0432.CCR-05-0661. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16166421)
- Goodenberger ML, Thomas BC, Riegert-Johnson D, Boland CR, Plon SE, ClendenningM, Win AK, Senter L, Lipkin SM, Stadler ZK, Macrae FA, Lynch HT, Weitzel JN, dela Chapelle A, Syngal S, Lynch P, Parry S, Jenkins MA, Gallinger S, Holter S,Aronson M, Newcomb PA, Burnett T, Le Marchand L, Pichurin P, Hampel H, TerdimanJP, Lu KH, Thibodeau S, Lindor NM. PMS2 monoallelic mutation carriers: the knownunknown. Genet Med. 2016 Jan;18(1):13-9. doi: 10.1038/gim.2015.27. Epub 2015 Apr9. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/25856668) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4834863/)
- Hendriks YM, Jagmohan-Changur S, van der Klift HM, Morreau H, van PuijenbroekM, Tops C, van Os T, Wagner A, Ausems MG, Gomez E, Breuning MH, Brocker-VriendsAH, Vasen HF, Wijnen JT. Heterozygous mutations in PMS2 cause hereditarynonpolyposis colorectal carcinoma (Lynch syndrome). Gastroenterology. 2006Feb;130(2):312-22. doi: 10.1053/j.gastro.2005.10.052. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16472587)
- Idos G, Valle L. Lynch Syndrome. 2004 Feb 5 [updated 2021 Feb 4]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews(R) [Internet]. Seattle (WA): University ofWashington, Seattle; 1993-2024. Available fromhttp://www.ncbi.nlm.nih.gov/books/NBK1211/ Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20301390)
- Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med. 2003Mar 6; 348(10):919-32. doi: 10.1056/NEJMra012242. No abstract available. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12621137)
- Peltomaki P. Lynch syndrome genes. Fam Cancer. 2005;4(3):227-32. doi:10.1007/s10689-004-7993-0. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16136382)
- Santucci-Darmanin S, Paquis-Flucklinger V. [Homologs of MutS and MutL duringmammalian meiosis]. Med Sci (Paris). 2003 Jan;19(1):85-91. doi:10.1051/medsci/200319185. French. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12836196)
- Senter L, Clendenning M, Sotamaa K, Hampel H, Green J, Potter JD, Lindblom A, Lagerstedt K, Thibodeau SN, Lindor NM, Young J, Winship I, Dowty JG, White DM, Hopper JL, Baglietto L, Jenkins MA, de la Chapelle A. The clinical phenotype ofLynch syndrome due to germ-line PMS2 mutations. Gastroenterology. 2008Aug; 135(2):419-28. doi: 10.1053/j.gastro.2008.04.026. Epub 2008 May 2. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18602922) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2759321/)

- 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 mismatchrepair system involved in Lynch syndrome. Int J Clin Oncol. 2019 Sep;24(9):1012.doi: 10.1007/s10147-019-01515-w. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/31368001)
- Ten Broeke SW, van der Klift HM, Tops CMJ, Aretz S, Bernstein I, Buchanan DD, de la Chapelle A, Capella G, Clendenning M, Engel C, Gallinger S, Gomez Garcia E, Figueiredo JC, Haile R, Hampel HL, Hopper JL, Hoogerbrugge N, von KnebelDoeberitz M, Le Marchand L, Letteboer TGW, Jenkins MA, Lindblom A, Lindor NM,Mensenkamp AR, Moller P, Newcomb PA, van Os TAM, Pearlman R, Pineda M, Rahner N,Redeker EJW, Olderode-Berends MJW, Rosty C, Schackert HK, Scott R, Senter L,Spruijt L, Steinke-Lange V, Suerink M, Thibodeau S, Vos YJ, Wagner A, Winship I,Hes FJ, Vasen HFA, Wijnen JT, Nielsen M, Win AK. Cancer Risks for PMS2-AssociatedLynch Syndrome. J Clin Oncol. 2018 Oct 10;36(29):2961-2968. doi:10.1200/JCO.2018.78.4777. Epub 2018 Aug 30. Erratum In: J Clin Oncol. 2019 Mar20;37(9):761. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/30161022) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6349460/)
- Truninger K, Menigatti M, Luz J, Russell A, Haider R, Gebbers JO, Bannwart F, Yurtsever H, Neuweiler J, Riehle HM, Cattaruzza MS, Heinimann K, Schar P, JiricnyJ, Marra G. Immunohistochemical analysis reveals high frequency of PMS2 defectsin colorectal cancer. Gastroenterology. 2005 May;128(5):1160-71. doi:10.1053/j.gastro.2005.01.056. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/15887099)
- Vaughn CP, Baker CL, Samowitz WS, Swensen JJ. The frequency of previouslyundetectable deletions involving 3' Exons of the PMS2 gene. Genes ChromosomesCancer. 2013 Jan;52(1):107-12. doi: 10.1002/gcc.22011. Epub 2012 Sep 25. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23012243)

Genomic Location

The *PMS2* gene is found on chromosome 7 (https://medlineplus.gov/genetics/chromosome/7/).

Last updated April 1, 2020