Constitutional mismatch repair deficiency syndrome

Constitutional mismatch repair deficiency (CMMRD) syndrome is a rare disorder that greatly increases the risk of developing one or more types of cancer in children and young adults. The cancers that most commonly occur in CMMRD syndrome are cancers of the colon (large intestine) and rectum (collectively referred to as colorectal cancer), brain, and blood (leukemia or lymphoma).

Almost all people with CMMRD syndrome develop cancer before age 18, generally in late childhood. The age of diagnosis varies depending on the cancer type; brain cancers, leukemia, and lymphomas tend to occur at younger ages than colorectal cancer in people with CMMRD syndrome. It is estimated that 20 to 40 percent of people with CMMRD syndrome who develop cancer will develop another cancer later in life.

People with CMMRD syndrome may develop multiple noncancerous (benign) growths (adenomas) in the colon that are likely to become cancerous (malignant) over time. Brain cancers in CMMRD syndrome often involve certain cells called glial cells, causing gliomas or glioblastomas. The most common blood cancer in CMMRD syndrome is called non-Hodgkin lymphoma, which affects white blood cells. Other cancers that can occur in CMMRD syndrome include cancers of the small intestine, urinary tract, or uterine lining (endometrial cancer).

Many people with CMMRD syndrome develop features similar to those that occur in a condition called neurofibromatosis type 1. These features include changes in skin coloring (pigmentation), which are characterized by one or more flat patches on the skin that are darker than the surrounding area (café-au-lait spots). Some affected individuals have freckling or patches of skin that are unusually light in color (hypopigmented). Rarely, people with CMMRD syndrome will develop a feature of neurofibromatosis type 1 called Lisch nodules, which are benign growths that often appear in the colored part of the eye (the iris). Lisch nodules do not interfere with vision. Some people with CMMRD syndrome are initially misdiagnosed with neurofibromatosis type 1.

Frequency

CMMRD syndrome is a rare disorder; more than 200 affected individuals have been reported in the scientific literature.

Causes

Mutations in the *PMS2* gene are the most common cause of CMMRD syndrome, and mutations in the *MLH1*, *MSH2*, or *MSH6* gene cause the remaining cases. These four genes are involved in repairing errors that occur when DNA is copied in preparation for cell division (a process called DNA replication). Because these genes work together to fix DNA errors, they are known as DNA mismatch repair (MMR) genes.

Mutations in any of these genes result in near or complete loss of functional protein. A shortage of one of these proteins eliminates mismatch repair activity and prevents the proper repair of errors that occur during DNA replication. The errors accumulate and disrupt other genes involved in important cellular processes such as controlling cell growth and division (proliferation). Uncontrolled cell growth 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 a 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.

Inheritance Pattern

CMMRD syndrome is inherited in an autosomal recessive pattern, which means having mutations in both copies of the gene greatly increases the risk of developing cancer. The parents of an individual with CMMRD syndrome each carry one copy of the mutated gene.

A single mutation in any of the genes associated with CMMRD syndrome generally leads to a different cancer predisposition syndrome called Lynch syndrome. Because the parents of an individual with CMMRD syndrome typically have a single copy of the mutated gene, they may have Lynch syndrome. Lynch syndrome increases the risk of many types of cancer, particularly colorectal cancer, but also cancers of the stomach, small intestine, gallbladder ducts, upper urinary tract, endometrium, brain, and skin. Unlike CMMRD syndrome, individuals with Lynch syndrome often develop these cancers in adulthood. Additionally, not all people with Lynch syndrome develop cancerous tumors, so a person with CMMRD syndrome might not have a history of cancer in their family.

Other Names for This Condition

- biallelic mismatch repair deficiency syndrome
- BMMRD
- mismatch repair cancer syndrome
- mismatch repair deficiency

Diagnosis & Management

Formal Diagnostic Criteria

- Durno C, Boland CR, Cohen S, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, Levin TR, Lieberman D, Robertson DJ, Rex DK. Recommendations on Surveillance and Management of Biallelic Mismatch Repair Deficiency (BMMRD) Syndrome: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2017 May;152(6):1605-1614. doi: 10.1053/j.gastro.2017.02.011. Epub 2017 Mar 28. Review.
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- Wimmer K, Kratz CP, Vasen HF, Caron O, Colas C, Entz-Werle N, Gerdes AM, Goldberg Y, Ilencikova D, Muleris M, Duval A, Lavoine N, Ruiz-Ponte C, Slavc I, Burkhardt B, Brugieres L; EU-Consortium Care for CMMRD (C4CMMRD). Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). J Med Genet. 2014 Jun;51(6):355-65. doi: 10.1136/jmedgenet-2014-102284. Epub 2014 Apr 15. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24737826

Genetic Testing Information

- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: Turcot syndrome
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0265325/
- National Cancer Institute: Genetic Testing for Inherited Cancer Susceptibility Syndromes
  https://www.cancer.gov/about-cancer/causes-prevention/genetics/genetic-testing-fact-sheet

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22constitutional+mismatch+repair+deficiency+syndrome%22+OR+%22mismatch+repair+deficiency%22

Other Diagnosis and Management Resources

- The University of Toronto Hospital for Sick Children: The International Biallelic Mismatch Repair Deficiency Consortium
  http://www.sickkids.ca/MMRD/patients-families/index.html

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Non-Hodgkin Lymphoma
  https://medlineplus.gov/ency/article/000581.htm
- Health Topic: Brain Tumors
  https://medlineplus.gov/braintumors.html
- Health Topic: Colorectal Cancer
  https://medlineplus.gov/colorectalcancer.html
- Health Topic: Leukemia
  https://medlineplus.gov/leukemia.html
- Health Topic: Lymphoma
  https://medlineplus.gov/lymphoma.html

Genetic and Rare Diseases Information Center

- Turcot syndrome
  https://rarediseases.info.nih.gov/diseases/420/turcot-syndrome

Additional NIH Resources

- National Cancer Institute: Genetic Testing for Inherited Cancer Susceptibility Syndromes
  https://www.cancer.gov/about-cancer/causes-prevention/genetics/genetic-testing-fact-sheet

Educational Resources

- MD Anderson Cancer Center: Glioblastoma
  https://www.mdanderson.org/cancer-types/glioblastoma.html
- Merck Manual Consumer Version: Overview of Brain Tumors
  https://www.merckmanuals.com/home/brain,-spinal-cord,-and-nerve-disorders/tumors-of-the-nervous-system/overview-of-brain-tumors
- Orphanet: Orphanet: Constitutional mismatch repair deficiency syndrome
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=252202
- St. Jude Children's Research Hospital
  https://www.stjude.org/disease/constitutional-mismatch-repair-deficiency.html

Patient Support and Advocacy Resources

- American Cancer Society: Colorectal Cancer
  https://www.cancer.org/cancer/colon-rectal-cancer.html
- Colorectal Cancer Alliance
  https://www.ccalliance.org/
- Fight Colorectal Cancer
  https://fightcolorectalcancer.org/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Colorectal+Neoplasms%5BMAJR%5D%29+AND+%28%28constitutional+mismatch+repair+deficiency+syndrome%5BTIAB%5D%29+OR+%28mismatch+repair+syndrome%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- MISMATCH REPAIR CANCER SYNDROME
  http://omim.org/entry/276300

Medical Genetics Database from MedGen

- Turcot syndrome
  https://www.ncbi.nlm.nih.gov/medgen/78553

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- Durno C, Boland CR, Cohen S, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, Levin TR, Lieberman D, Robertson DJ, Rex DK. Recommendations on Surveillance and Management of Biallelic Mismatch Repair Deficiency (BMMRD) Syndrome: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2017 May;152(6):1605-1614. doi: 10.1053/j.gastro.2017.02.011. Epub 2017 Mar 28. Review.
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- Sijmons RH, Hofstra RMW. Review: Clinical aspects of hereditary DNA Mismatch repair gene mutations. DNA Repair (Amst). 2016 Feb;38:155-162. doi: 10.1016/j.dnarep.2015.11.018. Epub 2015 Dec 11. Review.
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