OPEN ACCESS Freely available online

ISSN: 2161-1041
Hereditary Genetics: Current Research

Commentary

Lynch Syndrome Genes and Functions of DNA Mismatch Repair Proteins

Ellen Lopez*

Department of Hematology Oncology, Massachusetts General Hospital, Boston, USA

INTRODUCTION

Lynch syndrome, also known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC), is the most common inherited form of colorectal cancer, also significantly increasing the risk of other malignancies, such as endometrial, ovarian, gastric, and urinary tract cancers. This syndrome is caused by mutations in genes involved in the DNA Mismatch Repair (MMR) system, a critical mechanism for maintaining genomic integrity. Understanding the genes associated with Lynch syndrome and the functions of the MMR proteins they encode sheds light on the underlying biological processes that contribute to cancer development in affected individuals.

DESCRIPTION

The genetic basis of lynch syndrome

Lynch syndrome results from inherited mutations in one of several key genes involved in the DNA mismatch repair pathway. The main genes implicated in Lynch syndrome are *MLH1*, *MSH2*, *MSH6*, *PMS2*, and sometimes *EPCAM*, which indirectly affects MMR function. Mutations in these genes lead to a dysfunctional mismatch repair system, which allows errors that occur during DNA replication to accumulate, driving genomic instability and increasing cancer risk.

MLH1 (MutL Homolog 1): The *MLH1* gene is located on chromosome 3 and encodes a protein that forms a heterodimer with *PMS2*, known as MutLα. This heterodimer is essential for coordinating the repair of mismatched DNA base pairs. When errors are detected, MutLα facilitates the recruitment of additional repair proteins to excise and correct the mistakes. Mutations in *MLH1* are among the most common genetic causes of Lynch syndrome, leading to defective DNA repair and increased mutation rates in critical genes that control cell growth and division.

MSH2 (MutS Homolog 2): The *MSH2* gene is situated on chromosome 2 and encodes a protein that forms heterodimers with either MSH6 or MSH3 to create the MutSα and MutSβ complexes, respectively. MutSα, composed of *MSH2* and *MSH6*, is primarily responsible for recognizing single-base mismatches and small insertion-deletion loops. MutSβ, made of *MSH2* and *MSH3*, plays a role in identifying larger insertion-deletion mismatches. Mutations in *MSH2* disrupt the recognition of these replication errors, resulting in uncorrected DNA mutations and promoting cancer formation.

MSH6 (MutS Homolog 6): The *MSH6* gene, also located on chromosome 2, pairs with *MSH2* to form the MutSα complex. *MSH6* plays a critical role in the initial detection of base mismatches and small insertion-deletion errors during DNA replication. Although mutations in *MSH6* are less frequent than those in *MLH1* or *MSH2*, they still contribute significantly to Lynch syndrome, often presenting with a slightly lower risk for colorectal cancer but an elevated risk for endometrial cancer.

PMS2 (Postmeiotic Segregation Increased 2): The *PMS2* gene, found on chromosome 7, encodes a protein that partners with *MLH1* to form the MutLα complex. This complex is crucial for the donstream steps of the mismatch repair process, including the activation of endonuclease activity that makes incisions near the mismatch site, allowing for error correction. Mutations in *PMS2* are associated with Lynch syndrome, though they are generally less penetrant compared to *MLH1* or *MSH2* mutations. Nevertheless, carriers still have a considerable risk of developing various Lynch syndrome-associated cancers.

EPCAM (Epithelial Cell Adhesion Molecule): The *EPCAM* gene is located on chromosome 2 and is not directly involved in the mismatch repair process. However, deletions in the *EPCAM* gene can lead to the silencing of the adjacent *MSH2* gene through epigenetic mechanisms. As a result, individuals with *EPCAM* deletions experience a loss of *MSH2* function and a subsequent increase in the risk of Lynch syndrome-associated cancers. This highlights the complexity of genetic regulation and the interplay between adjacent genes in determining cancer susceptibility.

Correspondence to: Ellen Lopez, Department of Hematology Oncology, Massachusetts General Hospital, Boston, USA; E-mail: ellen.lopez@gmail.com

Received: 02-Nov-2024, Manuscript No. HGCR-24-27393; **Editor assigned:** 05-Nov-2024, PreQC No. HGCR-24-27393 (PQ); **Reviewed:** 19-Nov-2024, QC No. HGCR-24-27393; **Revised:** 14-Jun-2025, Manuscript No. HGCR-24-27393 (R); **Published:** 21-Jun-2025, DOI: 10.35248/2161-1041.25.14.312

Citation: Lopez E (2025) Lynch Syndrome Genes and Functions of DNA Mismatch Repair Proteins. Hereditary Genet. 14:312.

Functions of DNA mismatch repair proteins

The DNA mismatch repair system is fundamental to preserving genomic stability. During DNA replication, errors such as misincorporated nucleotides or small insertion-deletion loops can occur. These errors, if not corrected, can lead to mutations that disrupt cellular processes and contribute to cancer development. The MMR proteins work in a coordinated manner to identify and repair these mistakes, ensuring the accuracy of the genetic code.

Error recognition: The MMR process begins with the recognition of mismatches. The MutSα complex, consisting of *MSH2* and *MSH6*, scans newly synthesized DNA strands for base-pair mismatches and small loops. If a mismatch is detected, the MutSα complex binds to the error site and initiates the repair process. The MutSβ complex, composed of *MSH2* and MSH3, is responsible for identifying larger insertion-deletion loops. This recognition step is crucial for signaling downstream repair mechanisms.

Recruitment and coordination: Once a mismatch is identified, the MutS complex recruits the MutLα complex, made up of *MLH1* and *PMS2*. MutLα acts as a molecular matchmaker, coordinating the subsequent steps of the repair process. This includes the recruitment of exonucleases, which excise the erroneous DNA segment, and DNA polymerase, which synthesizes the correct DNA sequence. The coordination between MutS and MutL complexes ensures that the repair is efficient and accurate.

Implications of MMR deficiency

When mutations occur in MMR genes, the repair system fails to correct replication errors, leading to Microsatellite Instability (MSI), a hallmark of Lynch syndrome-associated tumors. Microsatellites are repetitive DNA sequences prone to replication errors, and the accumulation of mutations in these regions can disrupt genes that regulate cell growth, apoptosis, and DNA repair. Consequently, MMR deficiency fosters a mutator phenotype, accelerating the progression to malignancy.

CONCLUSION

Lynch syndrome is driven by mutations in genes encoding key DNA mismatch repair proteins. These proteins play vital roles in maintaining genomic stability by recognizing and correcting replication errors. When the MMR system is compromised, the resulting genetic instability predisposes individuals to various cancers, emphasizing the importance of genetic testing, early detection, and preventive strategies for at-risk families. Understanding the molecular mechanisms underlying MMR provides insights into targeted therapeutic approaches and cancer prevention in Lynch syndrome patients.