کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت‌های کاربردی در تدوین و چاپ مقاله
Genetics of Hereditary Nonpolyposis Colorectal Cancer

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Colorectal cancer is a major cause of morbidity and mortality. About 15 – 20% of all colorectal cancers are familial. Hereditary nonpolyposis colorectal cancer is an inherited cancer predisposition syndrome. It is caused by mutations in mismatch repair genes, predominantly MSH2 and MLH1. Although hereditary nonpolyposis colorectal cancer accounts for a minority of colorectal cancers, the mutations identified in these cases are important in our understanding of colorectal cancer pathogenesis. An increasing number of deletions in different exons of MSH2 and MLH1 genes is reported to result in hereditary nonpolyposis colorectal cancer. This paper reviews the genetics behind these genes and molecular study of the hereditary nonpolyposis colorectal cancer. This may help the medical professionals especially internists, gastroenterologists, and oncologists to update their knowledge in this field.

Keywords: Genetics • Hereditary Nonpolyposis Colorectal Cancer • MLH1 • MSH2

Introduction

Colorectal cancer (CRC) is one of the major causes of morbidity and mortality. It is the most common cause of early cancer death among nonsmokers in the west. CRC is the second cause of cancer death in the United States. It is difficult to rule out nonhereditary factors in CRC, as environmental factors (especially diet) play a significant role. This cancer typically presents around the age of 70 years and the risk of developing such a cancer increases with a positive family history.

Fifteen to 20% of all CRCs are familial. There are two well-defined genetic syndromes, familial adenomatous polyposis (FAP) in about 1% and hereditary nonpolyposis colorectal cancer (HNPCC) in about 5 – 8% of total CRC cases. In the majority of the familial cases, the underlying genes are still unknown. Investigating these two syndromes has helped to have a better insight into both inherited and sporadic types of human colorectal tumors.

Colon cancer is a mucosal disease. The mucosa is a single layer of columnar epithelial cells. This layer is the site of the earliest genetic alterations in the development of cancer cells.

History

HNPCC was described more than a hundred years ago when Warthin reported this cancer as a hereditary disease in a family that he studied from 1895. This observation was not fully appreciated until 1966 when two families were reported with an autosomal dominant pattern of nonpolyposis colorectal cancer and endometrial cancer. This cancer was first termed “cancer family syndrome”, then renamed as HNPCC. It has also been described as Lynch syndrome because Dr. Henry Lynch highlighted the importance of research done by Warthin. HNPCC can be clinically classified as Lynch I and Lynch II based on the absence or presence of extracolonic cancers.

Linkage analysis on two large kindreds discovered a linked microsatellite marker on chromosome 2 (D2S123) in many individuals who had colon cancer with or without endometrial cancer. Further evaluations showed a gene that was neither an oncogene nor a tumor suppressor gene, but could cause genomic instability.
Adenoma

Most CRCs seem to develop from adenomas.5 Both sporadic CRC and HNPCC tumors are believed to arise from preexisting adenomas as well. An important predictor for the presence of adenomas is the history of colon cancer in first-degree relatives. The strong predictors for developing carcinoma are size, number, and histologic features of adenomas.

Genetics of CRC

The process of carcinogenesis typically develops over decades and several mutations are required for completion. In CRC, at least four genetic changes need to occur. The main targets are an oncogene (K-ras) and three tumor suppressor genes (APC, DPC4, and p53).

Mapped to 12p12, K-ras belongs to the ras gene family and has a proposed function of growth signal transduction. Deleted in colon cancer (DCC) gene is mapped to 18q21 and has a function in cell adhesion. A heterozygous deletion of the DCC gene was detected in about 70% of CRC. DPC4 (deleted in pancreatic carcinoma) gene is a component of the TGFβ signalling pathway and shows a mutation in 50% of pancreatic cancers.6 The adenomatous polyposis coli (APC) gene mutation as a main cause of familial adenomatous polyposis will be discussed in more detail.

At least two forms of genetic instability have been detected in CRC: microsatellite instability (MSI) and chromosomal instability (CIN). In MSI tumors, the cells generally remain diploid and do not show an increased rate of chromosomal losses or gains compared with normal cells. Aneuploidy is the result of CIN, which is the case in most cancers and can be detected by classical chromosome banding studies and other molecular cytogenetic techniques. As a result of CIN and MSI, accumulation of specific genetic alterations happens, including activation of oncogenes and inactivation of tumor suppressor genes.

CIN tumors tend to be present at the left side of colon, especially in the rectosigmoid.2 These tumors have poor prognosis and aggressive behaviour, while MSI tumors have a significantly better prognosis.1

The genes involved in the development of CRC can be divided into two general categories based on their functions: the genes of the replication signalling pathway (K-ras, APC, and DCC) and the genes involved in maintaining DNA fidelity during replication (MSH2, MLH1, PMS1, PMS2, and p53).

Genes in CRC; gatekeeper and caretaker

Gatekeeper genes control tumorgenesis by inhibiting cell growth or promoting cell death. Mutations in gatekeepers can result in expanded clones of cells as targets for subsequent mutations. Caretaker genes permit cancer indirectly; their dysfunction causes mutations in other genes such as the gatekeepers. Mutations in caretakers cause defects in genome integrity and this instability can be seen at both nucleotide (defects in DNA replication or repair) and chromosomal levels (abnormal karyotype).

In CRC, APC is a gatekeeper, while the mismatch repair genes (MMR) are caretakers. P53 is both a caretaker (by protecting other genes against damage via halting the cell cycle to repair DNA) and a gatekeeper (its loss of function permits the transformation from adenoma to malignancy).

Familial adenomatous polyposis (FAP)

FAP (Mendelian inheritance in man number; MIM 175100) is an autosomal dominant (AD) condition with a frequency of about 1 in 10000 births.8 It is characterized by development of hundreds of polyps in the colorectal area, with a very high risk of malignancy. The onset of the polyp formation is usually in the second and third decades of life and its penetrance is nearly 100%. One or more of the polyps will, almost inevitably, progress to cancer, before 40 years of age unless it is excised by prophylactic colectomy.

The APC gene was firstly localized by linkage analysis of an interstitial deletion on chromosome 5 in a mentally retarded person with FAP in 1987.9 This tumor suppressor gene spans approximately 150kb with 15 exons. The proposed function of this gene is cell adhesion. FAP is caused by germline mutations in the APC gene.

Not only germline APC mutations are responsible for FAP but also somatic APC mutations are found in the majority (85%) of sporadic CRCs. This suggests that the loss of APC function is likely to play a role in CRC initiation. The mutated APC gene increases the cell growth speed and results in polyps.7 Pathogenic mutations in the APC gene have been detected in 70% of FAP patients. A frequent cause of FAP is submicroscopic deletions in exons of the APC
gene, which may be missed by standard mutation screening.\textsuperscript{10}

HNPPCC

HNPPCC (MIM 114500) is one of the most common hereditary diseases in humans.\textsuperscript{4} It can be defined by development of cancer in epithelial organs such as colorectum, endometrium, urinary tract, small intestine, ovary, stomach, and brain because of inactivation of DNA mismatch repair (MMR) genes.\textsuperscript{11} At least 5 – 8\% of CRCs are caused by HNPPCC, the most common form of hereditary CRC. In about 3\% of these cases, germline mutations in the MMR genes were detected. The mutations were unexplained for most of the remaining HNPPCC or HNPPCC-like kindreds.\textsuperscript{5}

An average age of 42 years is reported for the presentation of HNPPCC, which is more than two decades earlier than the age of CRC in general population.\textsuperscript{4} HNPPCC is a genetically heterogeneous disorder, with AD inheritance. It is characterized by early onset, mostly right-sided colorectal tumors proximal to the splenic flecture, and no earlier stage of polyposis. HNPPCC is an age-dependent condition, with a high penetrance. Three major hallmarks of HNPPCC are a family history of CRC or endometrial cancer, an early age of onset less than 50 years, and multiple primary cancers.\textsuperscript{12} The Muir-Torre syndrome (MIM 158320) is a variant of HNPPCC with sebaceous gland tumors and keratoacanthomas.\textsuperscript{8}

The MMR system controls the fidelity of DNA replication and maintains the integrity of the genome. HNPPCC patients generally inherit a germline mutation from one of the parents. At this level, the wild-type allele is sufficient to maintain adequate DNA repair. However, the second mutation (somatic mutation) of the wild-type allele leads to cancer progression.

HNPPCC diagnostic criteria

Having a guideline to define HNPPCC accurately is essential for cost-effective genetic testing. An international collaborative group on HNPPCC established “Amsterdam diagnostic criteria”\textsuperscript{13} in 1990. The criteria summarized as: 1) Three or more relatives in two successive generations with histologically verified colorectal adenocarcinoma, one of whom should be a first degree relative of the other two. 2) At least one relative diagnosed before the age of 50. 3) FAP should be excluded, either clinically or by DNA testing.

These criteria have some limitations; extracolonic cancers are not included, small families may not be indicated as HNPPCC, and there is a wide range in the age at diagnosis of cancer (15 to 75 years). There is no weight for distinctive pathologic features of HNPPCC; tendency for involving the proximal colon, and the special histologic findings.\textsuperscript{14} According to the “Amsterdam II criteria”, there should be at least 3 relatives with an HNPPCC-associated cancer (CRC, cancer of the endometrium, small bowel, ureter, or renal pelvis).

Briefly, in the “Bethesda criteria” all these cases are included: patients with positive Amsterdam criteria, individuals with two HNPPCC-related cancers, patients diagnosed before the age of 45 years suffering from CRC or endometrial cancer, right-sided CRC with an undifferentiated pattern on histopathology, and individuals with adenomas diagnosed before the age of 40 years.\textsuperscript{15}

Comparing these three criteria, it was concluded that the “Bethesda criteria” are the most sensitive guidelines to detect HNPPCC cases with pathogenic mutations in MSH2 and MLH1 genes.\textsuperscript{11}

Epidemiology of HNPPCC

The incidence of HNPPCC is unknown in the general population.\textsuperscript{8} In western population, 1 in 200 has this syndrome. Based on epidemiologic and genetic studies, it is estimated that HNPPCC is responsible for 0.5 to 13\% of CRCs. Carriers of MMR mutations have more than 80\% risk of cancer by the age of 75. This shows the importance of determining HNPPCC frequency in the population and to develop cost-effective detection approaches.\textsuperscript{12}

Microsatellite instability (MSI)

DNA MMR deficiency is the hallmark of HNPPCC. Most patients with HNPPCC show a replicative error phenotype (REP) caused by gains or losses of repetitive DNA sequences identified in tumour tissues. HNPPCC tumors are characterized by a high level of mutation in microsatellite repeat sequences in tumor DNA compared with normal genomic DNA from the same individuals. Short tandem repeats (STRs) or microsatellites are repeat sequences ranging from 2–6bp DNA that can be repeated up to 100 times. They vary in each person and have a range of in vivo mutation rate from 10\textsuperscript{-4}.
to $10^{-3}$ per generation.\textsuperscript{16} The main mutation mechanism of microsatellites is DNA replication slippage,\textsuperscript{17} which results in expansion or contraction of STRs. The mutation rate of (cytosine adenin; CA)$_n$ repeats in RER-positive tumour cells is at least 100 times more than RER-negative tumour cells.

The primary function of the MMR system is to remove base-base mismatches and insertion-deletion loops. Both of these events occur during DNA replication from DNA polymerase slippage. The detection of MSI in tumor DNA is indicative of genetic instability caused by loss of DNA MMR function and happens in about 15\% of sporadic colorectal and other tumors.\textsuperscript{18} Microsatellite length heterogeneity can be seen in multiple loci in colon tumors, which indicates that somatic genomic instability is a very early event in these cancers. MSI showed a negative correlation with p53, APC, and K-ras mutations.\textsuperscript{19} Mutations in these major growth regulatory genes promote the incidence of chromosomal aberrations and result in CIN. An analysis of MMR deficiency in sporadic CRC patients showed that 16.4\% of tumors were MSI positive.\textsuperscript{20}

\textbf{NSAIDs and HNPCC}

A cancer-preventive action has been detected for nonsteroidal antiinflammatory drugs (NSAIDs). This involves their antiproliferative and apoptosis-inducing activities. MSI in CRC cells deficient for the MMR genes is markedly reduced during exposure to aspirin or indomethacin.\textsuperscript{21} An induction of genetic selection for microsatellite stability (MSS) was suggested by these results. This may provide an effective prophylactic therapy for HNPCC kindreds.

\textbf{Extracolonic neoplasm in HNPCC}

In HNPCC, a broad spectrum of tissues is at risk of cancer. Endometrial cancer is the most common extracolonic neoplasm. The cumulative incidence of endometrial cancer is 60\% among female HNPCC mutation carriers by the age of 70 years.\textsuperscript{2} Significant increases were detected in cancers of the stomach, small intestine, the upper urologic tract (renal pelvis and ureter), and ovary in family members of those having HNPCC. There was no increased rate of cancers in the pancreas, breast, or urinary bladder.\textsuperscript{22} Turcot syndrome (MIM 276300) with brain tumors, colonic polyps, and colon cancer was shown to be in fact two syndromes. The APC gene involvement results in CRC, colonic polyps, and medulloblastomas, and MLH1 and PMS2 gene mutations causing CRC and glial malignancies.\textsuperscript{23}

\textbf{Genetics and molecular evaluation of HNPCC}

A hypothesis behind HNPCC formation is based on DNA repair. During DNA replication, some errors may be produced. Proofreading activity of DNA polymerase immediately corrects the errors. Overall proofreading activities reduce the rate of replication errors to about 1 per $10^{12}$bp. The process of MMR is required to recognize mismatched bases, insertions or deletions in the new strand, and to correct them. It is estimated that 99.9\% of the errors undetected by proofreading are repaired by this system.\textsuperscript{8}

Identification of mutations in affected HNPCC patients would be useful, because it helps to determine the carrier status of unaffected relatives at risk. The common reasons for referral to a medical genetic clinic are a family history of CRC especially with extracolonic features and/or early onset CRC with the absence of polyposis.\textsuperscript{24} The identification process begins with systematically recording the family history, highlighting all types of cancers and confirming them by medical documents. Since the tumors in HNPCC patients are indistinguishable from sporadic cases based on the numbers, morphologic, or histologic features, the syndrome is often undiagnosed if the family history is inadequate.\textsuperscript{1}

Testing for RER is recommended in all patients with CRC who have a family history of colorectal or endometrial cancer and an age of less than 50 years. Many laboratories use MSI analysis before looking for a gene mutation, because extramicrosatellite alleles can be seen in tumor DNA compared with matched normal DNA. Draft best practice guideline for molecular analysis of HNPCC recommends BAT26\textsuperscript{25} as marker for MSI.\textsuperscript{24} It is a poly (A) in MSH2 intron 5 and is monomorphic in normal tissue but has a high instability in HNPCC tumors. However, some laboratories analyze markers linked to MLH1 and MSH2. This draft suggests not screening further for germline mutations in cases with MSS.\textsuperscript{24}

As the most practical approach, MSI-positive patients should be considered for further analysis of germline mutations in MMR genes. It has been suggested to perform mutation screening in individuals diagnosed with CRC before the age of...
40 years. Genetic testing in MMR genes can detect gene carriers with the highest risk for CRC who can benefit from preventive approaches and discontinue these procedures in nondisposed family members.

In summary, the HNPCC screening test is usually based on two indicators; MSI and the loss of MMR protein expression, which is detected in more than 90% of these tumors.

At least five genes associated with HNPCC including MSH2, MLH1, MSH6, PMS1, and PMS2, which encode different components of a DNA MMR system. More than 90% of the identified mutations in HNPCC families are in MSH2 and MLH1 genes.

**MSH2**

Human MSH2 was cloned by PCR using degenerate oligonucleotide primers, which hybridized to highly conserved regions of yeast MSH2. Mapped to 2p22-p21, the gene covers approximately 73kb and contains 16 exons encoding a 935 amino acid protein (Figure 1). All identified germline mutations in Muir-Torre syndrome kindreds were linked to this gene. MSH2 protein is highly expressed in proliferative cells of the epithelium of esophagus, intestine, ileum, and colon.

**MLH1**

MLH1 was detected by amplification of human MutL related sequences. This gene (3p21) spans approximately 58kb with 19 coding exons (Figure 2) encoding a 756 amino acid protein.

**PMS1, PMS2, and MSH6**

Both postmeiotic segregation genes (PMS1 and PMS2) are the human homologues of yeast PMS gene. Germline mutations in the PMS1 or PMS2 were identified in a minority of HNPCC cases. The PMS1 and PMS2 genes are mapped to 2q31-q33 and 7p22, respectively.

MSH6 gene, initially called GT binding protein (GTBP), is located at 2p16. MSH6 encodes a protein that heterodimerizes with the MSH2 protein. Both proteins are required for mismatch specific binding. The presence of multiple endometrial cancers in a family is a characteristic of MSH6 mutations. In a minority of HNPCC cases, MSH6 mutations have been found.

**HNPCC mutation analysis**

Mutations have been detected in only 20 to 70% of HNPCC families, which indicate genetic heterogeneity. There are more than 300 different mutations predisposing to HNPCC. The majority of these mutations cause protein truncations, but missense mutations and large deletions are also reported. The mutation detection rate is up to 70% by direct sequencing of coding regions in the “Amsterdam criteria”-positive families. The sum of MSH2 and MLH1 mutations were found in a range from 45% to 86% of HNPCC patients. Adding the PMS1 and PMS2 genes in genetic tests tended to find a mutation in 70% of families. MSH2 and MLH1 mutations were detected in 49% of the families fulfilling the Amsterdam criteria. A pathogenic mutation was identified in only 8% of the families not fulfilling the criteria. It shows the importance of selecting appropriate families for research. Unlike FAP, there is no clear genotype-phenotype relationship in HNPCC.

There are various methods to screen the mutations in MMR genes such as direct sequencing, denaturing gradient gel electrophoresis (DGGE), reverse transcriptase polymerase chain reaction (RT-PCR), and protein truncation test (PTT). Direct sequencing of MMR genes is the “gold standard”. However, as a clinical approach, its role is limited by the nature of the genes and the heterogeneity of mutations. It is labor intensive and expensive to analyze the 35 exons of MSH2 and MLH1 genes. Also, large genomic deletions and small mutations involving primer-recognition sites may be missed.

DGGE can reveal point mutations with more than 90% efficiency and reproducibility. In DGGE, PCR products are electrophoresed through a polyacrylamide gel, and depending on the exon tested, there are various denaturing gradient ranges.

![Figure 1](https://www.SID.ir)
Changes in electrophoretic mobility can be determined by the presence of additional bands in which mutated exons can be detected and sequenced. However, the method may fail if there is a large genomic deletion or a mutation in a primer region. CpG dinucleotides within the coding regions of the MSH2 and MLH1 genes are hotspots for single base pair substitutions. Deletion of exon 5 of the MSH2 is a common MSH2 mutation suggested as a founder effect.

PTT can detect mutations resulting in alteration of the protein products size, such as deletion, insertion, and nonsense mutations. A T7 promoter sequence is introduced by extended primers used for PCR amplification to initiate transcription by T7 RNA polymerase. By this method a deletion of exon13 of MLH1 gene was detected.

In immunohistochemistry studies (IHC), tissue slides are stained with antibodies to either MSH2 or MLH1 proteins. This can help to indicate the involved gene for further mutation detection studies. An abnormal pattern of expression will be detected if tumor cells do not show nuclear staining, while the nonneoplastic stromal cells are normally stained.

There are different possible explanations for HNPCC families with undetected MSH2 or MLH1 mutations for example, conventional methods may miss rearrangements in MSH2 or MLH1, or the involvement of other MMR genes or some HNPCC cases are not related to a defect within the MMR system, and finally the promoter mutations.

**Genomic deletions**

Large deletions account for about 25% of all HNPCCs. Deletions might be often missed by conventional methods, so the protocols for screening the mutations in HNPCCs should be improved. Genomic deletions in these two genes reported in the Human Gene Mutation Database are summarized in Table 1.

Methods based on RNA such as RT-PCR and PTT may miss such rearrangements because of complete deletion of the gene or the instability of the altered mRNA. RT-PCR reveals a shorter transcript. However, large deletions may extend through the location of primers and therefore fail to produce a PCR fragment. Furthermore, RNA-based approaches need fresh blood samples, which are not available all the time.

Genomic deletions at MSH2 are frequent, with a rate of 6.5% of HNPCC cases defined by the Amsterdam criteria. It is detected in more than one third of all pathogenic MSH2 mutations among Dutch HNPCC families. So, screening for MSH2 rearrangements can be considered as the first step of molecular analysis in HNPCC.

Detection of large genomic deletions in these two genes was represented as a “technical problem”. A semiquantitative PCR assay was developed to detect the exonic rearrangements using short fluorescent fragments in a multiplex approach.

### Table 1. Some genomic deletions reported in MSH2 and MLH1 genes of patients with HNPCC cases.

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**Figure 2.** Diagram of MLH1 gene with the size of introns (in kb).
PCR. However, in this method four different PCRs were set up to cover all 35 exons and quantitative results were not presented.

The distribution of the rearrangements of MSH2 was consistent with the involvement of Alu-mediated recombination events. The majority of MSH2 rearrangements involved a region between the 5’ end of the gene and intron 8. This region is particularly rich in Alu repeats in which among the 105 Alu sequences identified in the gene, 88 were in the region between the promoter and exon 9. Based on multiplex PCR, modified with quantitative evaluation, novel deletions were identified. They concluded that MLH1 large genomic deletions might be frequent. MLH1 exon 16 deletion resulted from an Alu-mediated recombination was detected by RT-PCR, a founder mutation in Finland and Sweden. Multiples amplifiable probe hybridization (MAPH) was successfully applied for the analysis of copy number alterations in the exons of MSH2 and MLH1 genes. It is a simple and quick method for DNA copy number alterations. This method has also been applied to three other genetic syndromes; a developmental disorder (Holt-Oram syndrome) and two distinct peripheral neuropathies.

In the final point, it is worth mentioning two studies to clarify the importance of such molecular studies in Iran. A recent cancer registry was set out by collecting data on the incidence of colorectal tumors in five provinces of Iran. Age-adjusted rates of CRC in the Iranian males and females were 8.2 and 7.0/100,000, respectively. Another recent report by the same center showed that a total of 21 cases (4.7%) out of 449 CRC patients met the Amsterdam criteria II. They concluded that this relatively high frequency of HNPPC should be further confirmed with larger sample size, population based, and genetic studies.

There are several other studies highlighting the exonic deletion mechanism in MSH2 and MLH1 genes responsible for HNPPC.

Conclusion

More research is required to clarify the overall weight of different mutations in HNPPC cases, especially genomic deletions in MSH2 and MLH1 genes. Finding the responsible predisposing germline mutations will determine who is a candidate for participation in CRC surveillance and management programs.

References

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