History and Pathogenesis of Lynch Syndrome

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Abstract

Lynch syndrome is the familial clustering of colorectal and endometrial cancers. This syndrome is passed in an autosomal dominant fashion within families with defective mismatch repair as the genetic basis for cancer development in these patients. There remains a group of patients who fit clinical diagnostic criteria for an autosomal dominant familial cancer syndrome, which is phenotypically similar to Lynch syndrome, but for which no mismatch repair mutation is identified. Identification of alternate genetic mutations such as EPCAM and CHEK2 may explain the cancer risk in a small subset of these patients, but continuing work into the genetic basis of colorectal familial cancer syndromes is needed.

Keywords

- Lynch syndrome
- hereditary nonpolyposis colorectal cancer
- mismatch repair
- microsatellite instability
- CHEK2
- EPCAM

Objectives: On completion of this article, the reader should be able to describe the genetic basis for Lynch syndrome and recognize alternate genetic mechanisms that produce a Lynch-like phenotype.

History of Lynch Syndrome

Over a century ago, Dr. Warthin, a pathologist at the University of Michigan, described a family —"Family G." Family G had a predisposition for developing gastrointestinal as well as gynecologic cancers.[1,2] Dr. Warthin became interested in this family after his distraught seamstress expressed her conviction that she would most surely die of cancer at a young age. His detailed descriptions of this family and others with similar patterns of cancer development were published in an article in 1913.[2] Henry Lynch in 1961 published data from two family pedigrees who also had a clustering of similar cancers. A wide spectrum of cancers from Family N in Nebraska and Family M in Michigan were described with an autosomal dominant mode of inheritance.[2] One of the family members presented in delirium tremens and explained his alcoholism by stating, "Everyone in the family dies of cancer."[1]

In the mid-1980s this syndrome was named Lynch syndrome. It was then subdivided into Lynch I and Lynch II. Patients with Lynch I had colon and rectal cancer (CRC) only, whereas those with Lynch II developed CRC as well as extracolonic malignancies. As time progressed and more data were collected on the patients and their family members, it became clear that there was a significant overlap between the two groups. It was then termed hereditary nonpolyposis colorectal cancer (HNPCC) to differentiate it from familial adenomatous polyposis (FAP), which was known to present with hundreds of colorectal polyps.

As genetic testing and more specific classification systems were developed to further differentiate patients both genotypically and phenotypically, a clarification of the terms emerged. Lynch syndrome refers to patients who have an autosomal dominant inheritance of CRC and other cancers secondary to a genetic mutation in mismatch repair genes or tumor microsatellite instability. Patients with HNPCC are those who fit clinical diagnostic criteria (termed "Amsterdam criteria") for autosomal inheritance of a colorectal cancer syndrome, but do not have a defined genetic mutation.

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Genetic Basis of Lynch Syndrome

Lynch syndrome is an autosomally dominant inherited genetic disease. Microsatellite instability (MSI) is the hallmark of tumors in Lynch syndrome patients. Microsatellites are short mono, di, or trinucleotide repeats in a noncoding region throughout the human genome. There are over 200 microsatellite repeats located in the human genome.[3] Just like fingerprints, a patient's pattern of base pair microsatellites is unique. Intact DNA replication within a patient's cells maintains identical microsatellites in every cell. Tumors are defined as microsatellite unstable when tumor cells have microsatellites that differ from normal somatic tissue.

Extensive research has been performed on the cancers that develop in patients with Lynch syndrome. Tumors that have microsatellite instability develop in Lynch syndrome patients due to inheritance of a germline mutation in DNA mismatch repair mechanisms. The human body has several different mechanisms for repairing base pair mismatches in replicated DNA.

The initial function of DNA mismatch repair mechanisms was studied in single-cell organisms as early as the 1970s. It was found that occasionally DNA polymerase incorporates an incorrectly paired nucleotide during DNA replication. These errors most commonly occur in long, repetitive DNA sequences that are commonly seen in microsatellites. Mismatch repair mechanisms exist to correct these incorrectly paired nucleotides in newly replicated DNA.

Mismatch repair systems were first identified in prokaryotes. In single-cell yeast molecules there are three components to the DNA repair system. Jacob et al[4] described MutS, MutL, and MutH as working in concert to repair S-phase DNA replication errors. MutS first recognizes and attaches itself to the piece of DNA with the aberrantly placed nucleotide and creates a large loop. MutL then assists MutS in the repair complex.[5] MutH is an endonuclease that creates a nick in the DNA strand and allows DNA polymerase to resynthesize a new strand of correctly paired DNA.[2]

The human MMR system is slightly more complex. There are five known MutS genes (MSH2, MSH 3, MSH4, MSH5, MSH6) and four MutL genes (MLH1, PMS1, PMS2, MLH3).[6] At this time, there is no equivalent to the prokaryotic MutH. MSH2 forms heterodimeric complexes with both MSH3 and MSH6 and is responsible for recognizing the mismatch in base pairs or insertion/deletion loops. The loss of this gene causes a point or frame shift mutation that can lead to the creation of a nonfunctioning protein. These mutations accumulate in the areas of microsatellites that can be easily recognized when compared with the microsatellite regions of normal cells.[7,8] This genotypic expression is termed high microsatellite instability (MSI-H). Loss of MSH 6 or MSH 3 alone does not result in cancer formation as the aforementioned genes share redundant function. If both genes are nonfunctional then mutations can accumulate with subsequent cancer development. MLH1, which is similar to the prokaryotic MutL, forms a heterodimer with PMS2 to participate in the mismatch repair system; however, its exact function is not known. MLH1 also likely dimerizes with MLH3.[3] MLH1 and MSH2 are two of the most frequently mutated genes in Lynch syndrome tumors. This accounts for ~64% of mutations in patients diagnosed with Lynch syndrome.[9]

When MMR genes become mutated, several specific genes contain microsatellites in their coding region and become susceptible to the accumulation of mutations. Transforming growth factor β receptor type II (TGF β R II), insulin-like growth factor II receptor (IGFRII), and BAX are three of the most common. Ninety percent of tumors with MSI have either a mutation in TGF β R II or IGFRII. TGF β II R functions as a tumor suppressor to inhibit epithelial growth and ILGFR II activates TGF β R II. A mutation in either of these genes results in unopposed epithelial growth and cancer development. BAX is another gene that is commonly mutated in MSI H tumors. This gene has a long repeating guanine sequence that is very susceptible to frame shift mutations.[10] BAX exerts its effects in the process of apoptosis and is activated by p53. Of note, MSI H tumors are known to have stable wild-type p53 genes. Loss of function in either one of these individual genes can result in accelerated cancer development. In Lynch syndrome patients, there is evidence of genome wide point mutations or mismatches of up to 10 base pair insertion/deletion loops.[11]

MSI can occur in up to 10 to 15% of sporadic cancers. The development of MSI in these patients is not due to a germline mutation in their MMR system but results from an epigenetic phenomenon. These sporadic colorectal cancers are due to accumulated hypermethylation of MMR gene promoters. It is most commonly the MLH1 gene promoter that is methylated as a result of a sporadic BRAF mutation. These tumors are also diploid and carry an improved survival when compared with sporadic tumors that are microsatellite stable. Patients with sporadic cancers with MSI-H tumors have been found to be older than patients with Lynch syndrome and microsatellite stable (MSS) tumors. Kaker et al in 2002 reported that 50% of tumors that occurred on the right side of patients older than the age of 90 had evidence of methylation of the promoter region of MLH1.[12] A cohort of 257 consecutive colorectal cancer patients from the Mayo Clinic were tested for tumor microsatellite instability. Approximately 20% of the tumors were MSI-H and caused by a loss of MLH-1. However, only 2% were due to a germline mutation in MLH-1. Patients with germline MLH-1 mutations were younger when compared with patients who showed evidence of hypermethylation.[13]

Alternate Genetic Pathways to Lynch Syndrome

Historically, the underlying mechanism for Lynch syndrome is the result of an autosomal dominant DNA mismatch repair [MMR] deficiency with resultant tumor microsatellite instability [MSI]. However, there is recent evidence to suggest a role for other genes as yet unidentified, alternative genetic pathways unrelated to mismatch repair, and so-called modifier or accessory genes that might predispose to the development of Lynch syndrome. At the same time, it appears that

different genes are responsible for different phenotypes, as well as different extracolonic malignancies.

In recent years, alternative mechanisms have been identified and may explain the different phenotypes and incidences of extracolonic malignancies in Lynch syndrome. One such entity is that of EPCAM mutation. EPCAM (formerly known as TACSTD1) is a non-MMR gene that codes for epithelial cellular adhesion molecule CD 326. This is found on all normal epithelial cells and certain carcinomas. Germ-line deletions involving the 3′exon of EPCAM results in promoter hypermethylation, inactivation of the MSH2 gene, and subsequent development of multiple malignancies consistent with Lynch syndrome.[14,15] The MSH2 inactivation results in MSI, but may not affect all tissues. Therefore, patients with EPCAM mutations (conferring a Lynch phenotype) very frequently fail to show a pathogenic mismatch repair mutation and will be missed by tumor screening with immunohistochemical stain (IHC) for loss of MMR protein expression.

Current data suggests that 10 to 40% of the patients with early-onset colorectal cancer (mean age 43), and malignancies involving the duodenum, ileum, appendix, endometrium, and bladder may have an EPCAM mutation.[15] Conversely, there are other reports of EPCAM and a predominantly colorectal cancer phenotype, underscoring possible variable presentations for as yet unknown reasons.[16] These studies are small, and therefore lack power. When more patients with the EPCAM mutation are identified and studied, the role EPCAM plays in Lynch syndrome and the development of extracolonic malignancies will be defined.

Another intriguing mechanism for Lynch syndrome is the germ-line promoter hypermethylation of MLH1. It has been well reported that sporadic colorectal cancers may exhibit MSI as a result of somatic hypermethylation of MLH1. Neither germ-line or somatic hypermethylation will result in an identifiable mismatch repair mutation. The key differentiating factor is that sporadic cancers are the result of somatic hypermethylation rather than germ-line hypermethylation. The available data detailing malignancies and germ-line hypermethylation of MLH1 reveals the mean age at cancer diagnosis is 37. Perhaps most importantly, 9.4% of those proven to have Lynch syndrome (MMR mutation negative, but fulfill Amsterdam criteria) were due to the germ-line hypermethylation of MLH1 as an alternate pathway to Lynch syndrome.[15] The exact phenotype, tumor spectrum, and incidence remain to be defined for germ-line hypermethylation.

Cell cycle check point kinase 2 (CHEK2) is yet another alternative mechanism for early-onset cancer with a Lynch phenotype. CHEK2 is a serine\threonine kinase whose regulatory functions include cell cycle progression, apoptosis, DNA damage repair, and has been suggested to function as a genetic modifier for other susceptibility genes. CHEK2 has been associated with elevated breast cancer risks within the northern and central\eastern European populations (Finland, Poland, Germany, and Belorussian regions).[17] The risk of breast cancer secondary to CHEK2 mutation appears to be second only to BRCA mutations. There are four known CHEK2 variants with reports of two (CHEK2 I157T and CHEK2 1100DelC) that confer risks of multiple malignancies similar in presentation to Lynch syndrome. This pathway, for the most part, does not primarily involve MMR mutations, although there is some degree of overlap. Initial reports indicated that the 1100delC mutation carriers exhibited substantially higher rates of breast cancer, colon cancer, ovarian cancer, and various other Lynch-related malignancies. Further analyses revealed the same families fulfilled revised Amsterdam criteria, and that 4.2% carried both the 1100delC and a mismatch repair mutation.[18] This finding has led to consideration of an alternative pathway to Lynch syndrome, not previously identified. Since that time, there have been additional studies with somewhat conflicting data that are less suggestive of a direct correlation. However, at the very least, this does give consideration to 1100delC as a potential comodifier, with an as yet unidentified susceptibility gene, which confers significant familial clustering of malignancies similar to Lynch syndrome.[17–19]

Additional studies revealed that the CHEK2-I157T mutation was strongly associated with Lynch-related colorectal and extracolonic malignancies consistent with a more characteristic Lynch phenotype. This mutation has a wider distribution geographically; upon further evaluation, it revealed that 7.7% of those patients also carried mismatch repair mutations.[20] The limitations of these studies, and ultimately the conclusions, lie within the limited populations studied, and the fact that the inclusion parameters were based upon revised Amsterdam criteria. This very likely missed affected individuals and may have underrepresented the overlap of mismatch repair mutations, incidence of those affected, and extent of both colonic and extracolonic malignancies. There is, however, enough evidence to suggest some connection between 1100delC/I157T and the Lynch phenotype, which will undoubtedly become clearer with time and larger populations studied.

Conclusion

The original description of Lynch syndrome has led to 100 years of research and further refinement in the characterization and genetic basis for the disorder. The classic pathway for development of Lynch syndrome cancers is through the accumulation of mismatched bases in microsatellite areas of DNA secondary to an inherited defect in mismatch repair mechanisms. Other genetic mutations continue to be identified, which account for a smaller percentage of HNPCC cancers, but remain important for the diagnosis and screening of patients and their families.

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