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Review

Lynch Syndrome

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ABSTRACT

Lynch syndrome (LS) is an autosomal-dominant disease characterized by an increased cancer susceptibility, particularly of the colon and endometrium. LS is caused by a constitutional heterozygous loss-of-function mutation or epimutation in one of the DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6 or PMS2). Loss of MMR activity leads to an accumulation of DNA replication errors, especially in repetitive sequences, a phenomenon referred to as microsatellite instability (MSI). MSI occurs in the majority of LS cancers and is a hallmark of the disease. The lifetime risk of cancers in individuals with LS varies dependent on gender and on which MMR gene is mutated. Intensive colorectal screening is proven to be effective in reducing colorectal cancer-related mortality in LS patients.

Keywords
Lynch syndrome, Hereditary Non-polyposis Colorectal cancer, Colorectal cancer, HNPCC, MMR, Mismatch repair

Identity

Other names

Hereditary Non-polyposis Colorectal Cancer, HNPCC

Note

Inherited cancer susceptibility syndrome characterized by a high risk of developing colorectal, endometrial and other malignancies.

Inheritance

Autosomal dominant with incomplete penetrance and variable expressivity; the cumulative lifetime risk of cancers is gender-related and dependent on which MMR gene is mutated. The prevalence of LS has been estimated between one in 370 and one in 3.100 people of the general population (Stormorken et al., 2007; Jarvinen et al., 2009).

Clinics

Note

The term Lynch Syndrome is correctly applied to families and patients with a germline defect in one of the MMR genes; this designation is more appropriate than HNPCC (Hereditary Non-Polyposis Colorectal Cancer) because LS patients could develop also some colorectal polyps, which makes the word "nonpolyposis" ambiguous.

The MMR pathway normally maintains fidelity of the DNA during replication by correction of single

base pair mismatches and small insertion or deletion loops (Kunkel and Erie, 2005). LS-related cancers form when a somatic loss of the remaining wild type allele occurs; this results in loss of MMR activity and subsequent MSI in tumour tissue. The MSI, as well as the negative immunohistochemical staining for the protein encoded by the mutated MMR gene, occurs in over 90% of LS-related cancers.

Phenotype and clinics

Colorectal cancer(CRC) is the most common malignancy in LS patients. LS-associated CRCs are characterized by an early age of onset (44-61 years versus 69 years in sporadic cases (Giardiello et al., 2014)); this earlier presentation is related to a more rapid adenoma-carcinoma sequence. Moreover, CRCs in LS patients frequently occur on the right side of the colon (Lynch et al., 1993; Lynch and Smyrk, 1996; Aarnio et al., 1999) and tend to be mucinous, poorly differentiated and with tumour-infiltrating lymphocytes (Kastrinos and Stoffel, 2014). Noteworthy, a high rate of metachronous CRCs after segmental colectomy has been described with a cumulative risk of 16% at 10 years and 41% at 20 years (Parry et al., 2011).

Endometrial carcinoma (EC) is the second most frequent cancer occurring in women with LS and is characterized by a young age at onset, with an average age at diagnosis of 48 years compared with 62 years in sporadic EC (Vasen et al., 2014; Hampel et al., 2005).

LS patients are also predisposed to $ (generally intestinal-type) and ovarian cancer (particularly with endometrioid / clear cell histology), with a mean age at diagnosis of 56 and 42.5 years, respectively (Aarnio et al., 1997; Capelle et al., 2010; Watson et al., 2008; Helder-Woolderink et al., 2016).

Less common LS-related malignancies include those of the urinary tract (transitional cell carcinomas), small bowel, hepatobiliary tract, glioblastomas and cutaneous sebaceous neoplasms (Bonadona et al., 2011; Kohlmann and Gruber, 2014).

Differential Diagnosis

Familial CRC. This definition is used to describe families characterized by a cluster of CRCs not apparently related to a known hereditary CRC syndrome. Familial CRC is a heterogeneous condition that can be caused in part by a combination of genetic and environmental factors.

Attenuated familial adenomatous polyposis (AFAP). The attenuated form of APC-related polyposis is characterized by fewer polyps and later age of onset than classic FAP. Extracolonic manifestations (e.g., gastric and duodenal polyps, , dental anomalies, congenital hypertrophy of the retinal pigment epithelium and desmoid tumours) could be variably present. Polyps and CRCs associated with AFAP do not exhibit MSI

MUTYH-Associated polyposis (MAP). The colonic phenotype of MAP can be similar to attenuated FAP but the inheritance is autosomal recessive. A minority of individuals with MAP presented with CRC and few or no polyps (Croitoru et al., 2004: Farrington et al., 2005; Balaguer et al., 2007; Cleary et al., 2009).

Hamartomatous polyposis syndromes. These conditions are characterized by an increased risk of CRC but can be recognized by the presence of hamartomatous polyps and extracolonic manifestations.

Hereditary diffuse gastric cancer. CDH1-related gastric cancers are typically diffuse or with signet-ring histology.

BRCA1/BRCA2 hereditary breast-ovarian cancer. This condition should be suspected when the personal and/or family history includes ovarian cancer.

Neoplastic risk

In MLH1 and MSH2 gene mutation carriers, the lifetime risk of CRC ranges from 30% to 74% (Giardiello, 2014). Lower risk for CRC has been estimated in patients with MSH6 and PMS2 mutation, ranging from 10% to 22% (Hendriks et al., 2004; Senter et al., 2008).

EC occurs in up to 70% of women with MSH6 mutations; lower risks are described in those with MLH1 and MSH2 mutations (54%) and with PMS2 mutations (15%) (Giardiello et al., 2014; Hendriks et al., 2004; Senter et al., 2008).

Concerning ovarian cancer, the reported lifetime risks in women with LS range from 6.7% to 12% and appear to be higher for carriers of MSH2 mutations (Watson et al., 2008; Engel et al., 2012; Bonadona et al., 2011).

Gastric cancer is reported to occur in approximately 5%-13% of LS patients, with considerable variability based on country of origin (Watson et al., 2008; Capelle et al., 2010).

The risk for other LS-related cancers is lower, though increased over general population rates.

Treatment

Colorectal surveillance is the only surveillance protocol proved to be effective in LS patients. Colonoscopy is recommended every one to two years beginning between ages 20 and 25 years or two to five years before the earliest age of diagnosis in

the family, whichever is earlier (Giardiello et al., 2014; NCCN, 2017). Screening for CRC by colonoscopy has been shown to decrease CRC-related mortality by 72% (Dove-Edwin et al., 2005) and has been associated with lower risk of CRC and an earlier stage at diagnosis (Parry et al., 2011; Vasen et a., 2010; Engel et al., 2010; Stuckless et al., 2012).

The evidence for efficacy of surveillance for cancer of the endometrium, ovary, stomach, duodenum and urinary tract is limited.

Prophylactic removal of the colon is generally not recommended for individuals with LS because routine colonoscopy is an effective preventive measure. If a CRC is detected, full colectomy with ileorectal anastomosis might be considered because of the high risk for metachronous cancers. Prophylactic removal of the uterus and ovaries can be considered after childbearing is completed.

Growing but not conclusive evidence exists on the use of aspirin for prevention of cancer in LS patients (Burn et al., 2011; Rothwell et al., 2011). The potential benefits, risks and current limitations of available uncertainties of aspirin therapy should be discussed with LS patients.

Prognosis

Colonoscopic surveillance with early detection and treatment of invasive CRC is associated with excellent survival (Moller et al., 2015). When matched stage for stage, LS CRCs are associated with a better prognosis compared with sporadic CRCs (Watson et al., 1998; Gryfe et al., 2000).

LS-related EC or ovarian cancer have also a good prognosis when given current treatment (Moller et al., 2015).

Genes involved and proteins

Gene

MLH1 (mutL homolog 1)

Location

3p22.2

DNA/RNA

Description

The MLH1 gene is 72,558 bases in length, with 19 coding exons.

Transcription

The transcribed mRNA has 2524 bps. 12 distinct transcripts have been described.

Protein

Description

Size: 756 aminoacids; Molecular Mass: 84,601 Da. It contains an ATPase domain and three interaction domains, one for MutS homologs, one for PMS2, MLH3 or PMS1 and the other for EXO1.

Expression

Ubiquitous

Localisation

Nucleoplasm

Function

The MLH1 protein dimerizes with PMS2 protein to form MutL alpha, a component of the post-replicative DNA mismatch repair (MMR) system. The MutL alpha heterodimer possesses an endonucleolytic activity that is activated following the recognition of DNA mismatches and insertion/deletion loops by MutS alpha (composed of MSH2 and MSH6) or MutS beta (composed of MSH2 and MSH3). MutL-MutS complex is responsible for the recruitment of other proteins involved in MMR.

The MLH1 protein can also bind to PMS1 or MLH3 to form MutL beta and MutL gamma respectively. MutL beta and gamma heterodimers are probably components of the MMR system.

Homology

MLH1 is homolog of the E. coli DNA mismatch repair gene mutL and MLH1 homologs are also present in eukaryotes.

Mutations

Germinal

More than 200 different pathogenic variants have been reported. MLH1 mutations are responsible of 35-40% cases of Lynch Syndrome (LS). Nonsense, missense and splice-site mutations predominate, whereas large genomic rearrangements constitute A and exon 16 deletion account for 50% of LS families in Finland) (Lynch et al., 2009).

Somatic

The most frequent cause of microsatellite instability (MSI) and loss of MLH1 and PMS2 immunohistochemical expression is the somatic methylation of the promoter region of MLH1 that silences gene expression in the tumour tissue.

Epigenetics

Constitutional inactivation of MLH1 by hypermethylation has been reported as a rare cause of LS (< 1%). Most of such cases are sporadic and not heritable, but a few cases of inherited hypermethylation have been reported (Goel et al., 2011; Peltomaki, 2014; Hitchins, 2016).

Gene

MSH2 (mutS homolog 2)

Location

2p21-p16.3

DNA/RNA

Description

he MSH2 gene is 159,343 bases in length, with 16 coding exons.

Transcription

The transcribed mRNA has 3145 bps. 9 distinct transcripts have been described.

Protein

Description

Size: 934 aminoacids; Molecular Mass: 104,743 Da. It contains a DNA binding domain and two interaction domains, one for MSH3 or MSH6 and the other for MutL homologs (composed of MLH1 and PMS2).

Expression

Ubiquitous

Localisation

Nucleoplasm.

Function

The MSH2 protein forms an heterodimer with either MSH6 (MutS alpha) or MSH3 (MutS beta) and identifies DNA mismatches. While MutS alpha complex recognizes single base mismatches and dinucleotide insertion-deletion loops in the DNA, MutS beta recognizes larger insertion-deletion loops. A sliding clamp model has been suggested to describe the structure of these heterodimers.

After mismatch binding, MutS alpha or beta associates with the MutL alpha heterodimer (composed of MLH1 and PMS2): MutL-MutS complex is responsible for the recruitment of other proteins involved in MMR.

Homology

MSH2 is homolog of the E. coli DNA mismatch repair gene mutS and MSH2 homologs are also present in eukaryotes.

Mutations

Germinal

More than 170 different pathogenic variants have been reported. MSH2 mutations are responsible of 44-48% cases of Lynch Syndrome (LS). Nonsense, missense and splice-site mutations predominate, but large genomic rearrangements constitute >20% of the alterations. The higher proportion of Alu repeats may contribute to the higher rate of genomic rearrangements in MSH2 than in MLH1. There are also MSH2 founder mutations which account for a high proportion of LS families in some specific populations (e.g. exons 1-6 deletion in United States) (Lynch et al., 2009).

Somatic

Microsatellite instability (MSI) and loss of MSH2 and MSH6 immunohistochemical expression can also be due to somatic mutations in MSH2 gene.

Epigenetics

Germline deletions of the 3' end of EPCAM gene can lead to inactivation of the MSH2 promoter through hypermethylation and, therefore, are a rare cause of LS (< 3%).

Gene

MSH6 (mutS homolog 6)

Location

2p16.3

DNA/RNA

Description

The MSH6 gene is 23,871 bases in length, with 10 coding exons.

Transcription

The transcribed mRNA has 4263 bps. 10 distinct transcripts have been described.

Protein

Description

Size: 1360 aminoacids; Molecular Mass: 152,786 Da. It contains a highly conserved helix-turn-helix domain associated with a Walker-A motif (an adenine nucleotide and magnesium binding motif) with ATPase activity.

Expression

Ubiquitous

Localisation

Nucleoplasm

Function

The MSH6 protein dimerizes with MSH2 to form MutS alpha and functions in the identifications of single base mismatches and dinucleotide insertion-deletion loops in the DNA by a sliding clamp model.

MutS alpha associates with the MutL alpha heterodimer (composed of MLH1 and PMS2): MutL-MutS complex is responsible for the recruitment of other proteins involved in MMR.

Homology

MSH6 is homolog of the E. coli DNA mismatch repair gene mutS and MSH6 homologs are also present in eukaryotes.

Mutations

Germinal

More than 30 different pathogenic variants have been reported. MSH6 mutations are responsible of 8-10% of cases of Lynch Syndrome. Nonsense, missense and splice-site mutations predominate, whereas large genomic rearrangements are rare.

Somatic

The involvement of somatic or epigenetic inactivation of MSH6 is rare.

Gene

PMS2 (PMS1 homolog 2, mismatch repair system component)

Location

7p22.1

DNA/RNA

Description

The PMS2 gene is 35,887 bases in length, with 15 coding exons.

Transcription
The transcribed mRNA has 2771 bps. 3 distinct transcripts have been described.

Pseudogene
Multiple pseudogenes have been identified at 7p22, 7p12-13 and 7q11 (Nicolaides et al., 1995).

Protein

Description
Size: 862 aminoacids; Molecular Mass: 95,797 Da. It contains a region of homology with other MutS or MutL homologs, comprising a region of 150 aminoacids encompassing a putative helix-turn-helix domain associated with an adenine nucleotide and magnesium binding sites.

Expression
Ubiquitous.

Localisation
Nucleoplasm.

Function
The PMS2 protein dimerizes with MLH1 to form MutL alpha, a component of the post-replicative DNA mismatch repair (MMR) system. The MutL alpha heterodimer possesses an endonucleolytic activity that is activated following the recognition of DNA mismatches and insertion/deletion loop by MutS alpha (composed of MSH2 and MSH6) or MutS beta (composed of MSH2 and MSH3). MutL-MutS complex is responsible for the recruitment of other proteins involved in MMR.

Homology
The PMS2 gene is homolog to yeast mutator gene (bacterial mutL) and PMS2 homologs are also present in eukaryotes.

Mutations

Germinal
Germline pathogenic variants in PMS2 are rare and are responsible of 2-8% cases of Lynch Syndrome. Single nucleotide variants and large gene rearrangements have been reported. Large rearrangements may constitute >20% of the alterations.

Somatic
The involvement of somatic or epigenetic inactivation of PMS2 is rare.

Gene

EPCAM (tumor-associated calcium signal transducer 1)

Location
2p21

DNA/RNA

Description
The EPCAM gene is 42,444 bases in length, with 9 coding exons.

Transcription
The transcribed mRNA has 1731 bps. 3 distinct transcripts have been described.

Pseudogene
One pseudogene in 4q34.3.

Protein

Description
Size: 314 aminoacids; Molecular Mass: 34,932 Da. It contains a thyroglobulin type 1 repeat, two epidermal growth factor-like extracellular domains, one single transmembrane domain, one small intercellular domain (EpICD), that alone is sufficient to induce proliferation signals and PDZ-domain identified in its C-terminal end.

Expression
Highly and selectively expressed by undifferentiated rather than differentiated embryonic stem cells. Levels rapidly diminish as soon as embryonic stem cells differentiate. Expressed in almost all epithelial cell membranes but not on mesodermal or neural cell membranes (Litvinov et al., 1996).

Localisation
Plasma membrane; baso-lateral in normal cells; redistribution on entire plasma membrane in vitro and in carcinoma cells.

Function
This gene encodes a carcinoma-associated antigen and functions as a hemophilic calcium-independent cell adhesion molecule. EPCAM plays also a role in embryonic stem cell proliferation and differentiation.

Homology
EPCAM homologs are also present in eukaryotes.

Mutations

Germinal
Deletions involving the transcription termination signal of EPCAM can lead to inactivation of the MSH2 promoter through hypermethylation and, therefore, are a rare cause of Lynch Syndrome. Other EPCAM pathogenic variants that do not affect the transcription termination signal cause autosomal recessive congenital tufting enteropathy.

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