Oxford Molecular Genetics Laboratory

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Lynch syndrome (Hereditary Non-Polyposis Colorectal Cancer (HNPCC)) – OMIM #120435 120436 (*MLH1*), 609309 (*MSH2)*, 600678 (*MSH6*)

INTRODUCTION

Lynch syndrome (also known as HNPCC) is an autosomal dominant cancer predisposition syndrome characterised by colorectal adenocarcinomas and other cancers including; endometrial, ovary, stomach, urinary tract and brain.
The mean age of onset for Lynch syndrome is ~45yrs, but it can develop as early as teenage. Age related penetrance is seen in Lynch syndrome mutation carriers but the lifetime risk for of developing an associated cancer is ~70-80%. Women are at higher risk of developing endometrial cancer than colorectal cancer.
Lynch syndrome is caused by inactivating mutations in the mismatch repair (MMR) genes, resulting in defective DNA mismatch repair which may often be detected by microsatellite instability (MSI) within tumour DNA.
Approximately 98% of Lynch syndrome is caused by pathogenic mutations in the genes, *MLH1, MSH2* and *MSH6*.

TESTING

Diagnostic:	Clinically affected patients.
Presymptomatic:	Individuals at risk of developing Lynch syndrome. Clinically unaffected relatives of individuals in whom a pathogenic MMR gene mutation has been identified.

REFERRALS

- All diagnostic & presymptomatic cases must be referred through Clinical Genetics departments.
- Diagnostic referrals should meet a minimum of “Modified Amsterdam Criteria”.
- Requests for presymptomatic testing should either be discussed with the laboratory in advance or be accompanied by details regarding the known pathogenic mutation in the family.

STRATEGY

- Diagnostic testing includes screening of the entire coding region and intron/exon boundaries of the *MLH1*, *MSH2* and *MSH6* genes and dosage analysis for large scale rearrangements of these 3 genes and the *EpCAM* gene, which is upstream of *MSH2* (Kovacs et al. 2009, Human Mutation, 30(2):197-203).
- In mutation negative cases showing loss of MSH2 and MSH6 on immunohistochemistry, testing for a previously reported inversion of *MSH2* can be conducted (Rhees et al. 2014, Familial Cancer, 13:219-225).
- When a pathogenic mutation has been identified in an individual, subsequent testing of family members (presymptomatic or diagnostic confirmation) involves testing for the familial mutation only.

TECHNICAL INFORMATION

- Mutation screening is undertaken by direct fluorescent sequencing of the entire coding region and intron/exon boundaries of *MLH1, MSH2* and *MSH6*. Dosage analysis is carried out by MLPA (multiplex ligation-dependant probe amplification) of the *MLH1*, *MSH2* and *MSH6* genes and the *EpCAM* gene which is upstream of *MSH2;* using kits P003-B2 and P072-B2 from MRC-Holland.
- MSI analysis and immunohistochemistry of tumour samples may assist in the diagnosis of Lynch syndrome particularly in patients who fail to meet the testing criteria or patients in whom no *MSH1/MSH2* mutation has been found. MSI analysis is available in this laboratory and IHC analysis is available in cellular pathology.

CLINICAL SENSITIVITY

Germline *MLH1* and *MSH2* mutations account for ~90% of mutations in families with Lynch syndrome; *MSH6* mutations ~7%-10%; and *PMS2* mutations in fewer than 5%. Germline deletions in *EPCAM* (not a MMR gene) inactivate *MSH2* in ~1% of individuals with Lynch syndrome (Kohlmann, 2014 http://www.ncbi.nlm.nih.gov/books/NBK1211/).

TARGET REPORTING TIMES

Diagnostic test (3 gene screen):	40 working days
Presymptomatic/Familial Mutation test:	10 working days

N.B. Details are correct for the date of printing only – last update 11/06/2015