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# Prevalence of germline *MUTYH* mutations among Lynch-like syndrome patients

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*KRAS* mutations

**Abstract** ***Background and aims:*** Individuals with tumours showing mismatch repair (MMR) deficiency not linked to germline mutations or somatic methylation of MMR genes have been recently referred as having 'Lynch-like syndrome' (LLS). The genetic basis of these LLS cases is unknown. *MUTYH*-associated polyposis patients show some phenotypic similarities to Lynch syndrome patients. The aim of this study was to investigate the prevalence of germline *MUTYH* mutations in a large series of LLS patients.
***Methods:*** Two hundred and twenty-five probands fulfilling LLS criteria were included in this study. Screening of *MUTYH* recurrent mutations, whole coding sequencing and a large rearrangement analysis were undertaken. Age, sex, clinical, pathological and molecular characteristics of tumours including *KRAS* mutations were assessed.
***Results:*** We found a prevalence of 3.1% of MAP syndrome in the whole series of LLS (7/225) and 3.9% when only cases fulfilling clinical criteria were considered (7/178). Patients with *MUTYH* biallelic mutations had more adenomas than monoallelic ($P = 0.02$) and wildtype patients ($P < 0.0001$). Six out of nine analysed tumours from six biallelic *MUTYH* carriers harboured *KRAS*-p.G12C mutation. This mutation was found to be associated with biallelic *MUTYH* germline mutation when compared with reported series of unselected colorectal cancer cohorts ($P < 0.0001$).
***Conclusions:*** A proportion of unexplained LLS cases is caused by biallelic *MUTYH* mutations. The obtained results further justify the inclusion of *MUTYH* in the diagnostic strategy for Lynch syndrome-suspected patients.


## 1. Introduction

About 1–5% of colorectal cancers (CRCs) are caused by germline mutations or epimutations in mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6* and *PMS2* [1]. This disorder is named the Lynch syndrome (LS) and is characterised by an autosomal dominant inheritance, a predisposition to early onset CRC and an increased risk of other cancers [1].

Molecular diagnosis of LS is well established and is mainly based in the use of clinical criteria to identify those patients with CRC candidate for molecular analysis [2]. Tumours of candidate patients are analysed for the presence of microsatellite instability (MSI) and/or loss of expression of MMR proteins by immunohistochemistry (IHC) as a screening method to evidence MMR deficiency. Whenever MSI or MMR protein loss is present in the absence of *BRAF* mutation or *MLH1* methylation, germline mutational analysis is offered [3,4]. While the diagnostic yield of the molecular diagnosis of LS is good [5], it can certainly be improved. The overall mutation detection rate in pre-selected patients ranges from 30% to 78%, depending on the inclusion criteria applied [5–9]. In a highly selected series of Amsterdam families with MSI, the percentage of mutation detection may be as high as 95% [10]. However, failure to identify a pathogenic germline mutation in MMR genes does not exclude a hereditary cancer predisposition. Individuals with tumours showing MMR deficiency not linked to germline mutations or somatic methylation of MMR genes have been recently referred to as having 'Lynch-like syndrome' (LLS) [11].

*MUTYH* (OMIM*604933) encodes for a base excision repair DNA glycosylase [12]. Mutations in this gene cause the *MUTYH*-associated polyposis (MAP) syndrome, an autosomal recessive inherited condition commonly characterised by the presence of few to hundreds of colonic adenomatous polyps and an increased CRC risk at young age [12].

It has been reported that MAP patients show some phenotypic similarities to LS patients. In this regard, the extracolonic tumour spectrum is similar in both groups and CRC can be diagnosed in the absence of polyps or associated with a small number of polyps (reviewed in [13]). Moreover, MAP CRCs share some histological similarities with LS carcinomas and are associated with better prognosis [13]. At the protein level, human MUTYH is physically associated with MSH2/MSH6, and the MSH2/MSH6 complex stimulates the DNA binding and glycosylase activities of MUTYH with oxoG:A mispairs [14]. However, deficiency on MMR system is not frequently involved in MAP tumours [15–18], and MSI has been reported in very few CRCs from biallelic *MUTYH* carriers [15,18–21].

The aim of this study was to investigate the prevalence of germline *MUTYH* mutations in a Spanish series of patients considered as having LLS, with MMR-deficient tumours without identified germline MMR mutations. Our study confirms that biallelic germline