Lynch syndrome

- Vaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) in Risk-Reducing Gynecologic Cancer Surgery: A New Frontier in Hereditary Cancer Prevention
- Validation of a Digital Tool That Uses National Testing Guidelines to Identify Individuals at Risk for Hereditary Cancer
- Missed opportunities: Germline testing following tumor sequencing
- Genetic profiling of inherited colorectal cancer syndromes in Tunisian patients
- PMS2 c.2117del (p.Lys706Serfs*19) is the Most Frequent Cancer-Associated Founder Pathogenic Variant in the French-Canadian Population of Quebec, Canada
- Molecular surveillance-informed personalized multidisciplinary therapy achieves prolonged survival in a patient with Lynch syndrome-associated colorectal cancer: A case report
- Second malignancies in patients with deficient mismatch repair system/microsatellite instability-high colorectal cancer
- The Effect of X rays on the Expression of Mismatch Repair Genes and Proteins in Lynch Syndrome Associated Human Colorectal Cancer Cell Lines

Lynch syndrome (also known as Hereditary Non-Polyposis Colorectal Cancer, or HNPCC) is an autosomal dominant inherited disorder that significantly increases the risk of developing several types of cancer, most notably colorectal cancer and endometrial cancer.

Cause

Lynch syndrome is caused by germline mutations in DNA mismatch repair (MMR) genes, which are responsible for correcting replication errors:

MLH1

MSH2

MSH6

PMS2

Sometimes, deletions in EPCAM, which lead to epigenetic silencing of MSH2

Pathophysiology

Defective mismatch repair leads to microsatellite instability (MSI), an accumulation of mutations in repetitive DNA sequences, increasing the risk of malignant transformation.

Associated Cancers

Colorectal cancer (proximal colon predominance)

Endometrial cancer Ovarian cancer Stomach cancer Small bowel cancer Hepatobiliary tract cancer Urinary tract (especially upper urothelial) cancer Pancreatic cancer Brain (glioblastomas; Turcot variant)

Clinical Criteria

Amsterdam II Criteria: 3 affected relatives, 2 generations, 1 diagnosed <50 years, and FAP excluded Revised Bethesda Guidelines: for identifying who should undergo MSI testing

🛛 Diagnosis

Microsatellite instability (MSI) testing Immunohistochemistry (IHC) for MMR proteins

Germline genetic testing

Management

Regular colonoscopic surveillance starting at age 20-25

Endometrial and ovarian cancer screening (consider prophylactic hysterectomy/oophorectomy)

Aspirin chemoprevention (CAPP2 study suggests benefit)

Genetic counseling for relatives

A case of a pediatric patient diagnosed with MB based on clinical and pathological findings, which was further characterized as a TP53-mutant, SHH-activated MB through next-generation sequencing (NGS) and methylation profiling. His tumor was found to harbor a somatic MSH2 mutation and a suspected pathogenic germline MLH1 heterozygous variant. Simultaneously, the tumor exhibited microsatellite instability-high (MSI-H) and an exceptionally elevated tumor mutation burden (TMB = 297.17 Mut/Mb).

The presence of the MLH1 germline variant in the patient's mother and maternal grandmother was confirmed by sequencing, and the patient's maternal grandmother had a history of colorectal cancer. Ultimately, the patient was diagnosed with MB associated with LS. This case is the third case of Lynch syndrome with medulloblastoma, which contributes additional evidence to the cancer spectrum associated with LS and presents a novel avenue for patient treatment ¹⁾.

1. Strengths of the Case Report Comprehensive Molecular Characterization: The authors provide a thorough analysis using next-generation sequencing (NGS) and methylation profiling, which accurately classified the medulloblastoma (MB) as TP53-mutant, SHH-activated, a subgroup with well-documented clinical relevance and poor prognosis.

Multimodal Genetic Insight: The report demonstrates a multifaceted genomic disruption: somatic MSH2 mutation, germline MLH1 heterozygous variant, MSI-H, and ultra-high TMB (297.17 Mut/Mb). These features suggest a strong deficiency in the DNA mismatch repair (MMR) system, aligning with a diagnosis of Lynch syndrome (LS).

Familial Genetic Confirmation: Identification of the MLH1 germline variant in two generations (mother and maternal grandmother) and the associated history of colorectal cancer in the grandmother robustly support the LS diagnosis.

Rare Association: This is reported as the third known case linking LS with MB. Given the rarity of this co-occurrence, the case contributes novel evidence to the LS tumor spectrum, previously dominated by colorectal, endometrial, and urothelial cancers.

2. Limitations and Weaknesses Incomplete Functional Validation: The report refers to a "suspected pathogenic germline MLH1 variant" but lacks functional validation (e.g., IHC for MMR proteins, promoter methylation testing, or in silico predictive modeling). The pathogenicity should be better substantiated to strengthen the LS link.

Therapeutic Implications Underdeveloped: Despite the high TMB and MSI-H, which are potential predictors of response to immune checkpoint inhibitors, the case does not elaborate on treatment considerations, clinical decisions, or follow-up outcomes. These would enrich the translational value.

Limited Discussion on TP53 Mutation Interplay: The tumor is TP53-mutant, which is mutually exclusive with TP53 germline mutations in Li-Fraumeni syndrome. However, the report does not explore whether this mutation alters the clinical course or overlaps with DNA repair pathway dysregulation.

Epidemiological Context Missing: The rarity of LS-associated MB is emphasized, but the mechanistic rationale or plausible explanations for SHH-MB development in the context of MMR deficiency are not discussed. This weakens the hypothesis of a causal link beyond coincidence.

3. Scientific and Clinical Relevance This case is scientifically significant for:

Supporting the expansion of the LS tumor spectrum to include MB (specifically SHH subtype),

Highlighting the importance of germline testing in pediatric tumors with high TMB and MSI,

Raising awareness of immunotherapy-sensitive signatures in rare pediatric CNS tumors.

However, the case falls short of integrating these findings into clinical actionability, particularly in terms of precision medicine interventions and family counseling beyond the molecular diagnosis.

Conclusion This report adds meaningful data to a sparsely documented oncogenetic overlap—MB and LS—but would benefit from deeper functional validation, therapeutic extrapolation, and mechanistic discussion. It is hypothesis-generating, not confirmatory, and should be viewed as a rare but plausible example of MMR-deficiency manifesting in a non-canonical tumor type.

Recommendation: Future reports should systematically include IHC, detailed variant curation, longitudinal outcomes, and treatment response, especially when proposing rare syndromic associations.

1)

Zheng H, Zhang G, Jiang B, Zhang L, Duan Q, Shi H. Medulloblastoma associated with Lynch syndrome: a case report of germline MLH1 variant and tumor molecular characterization. Invest New Drugs. 2025 May 19. doi: 10.1007/s10637-025-01527-6. Epub ahead of print. PMID: 40388014.

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