Immunohistochemistry Division
8267 Elmbrook, Suite 100, Dallas, Texas 75247-4009
Lab (214) 638-2000, ext 2037, Fax (214) 237-1730
Website: www.propathlab.com E-mail: rmiller@propathlab.com

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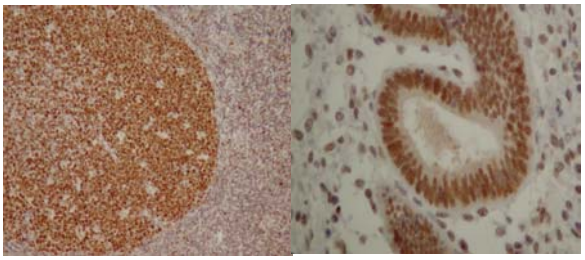
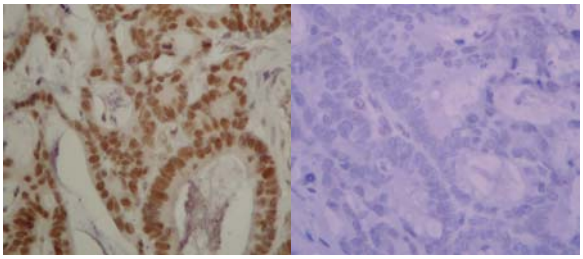
hMLH1 and hMSH2: Important Immunohistochemical Markers for the Evaluation of Patients with Possible Hereditary Non-Polyposis Colon Cancer Syndrome

Mismatch repair genes perform an essential cellular function by repairing DNA mismatches that may occur during cellular replication. A number of these genes have been identified in the human genome, including hMLH1, hMSH2, hMSH3, hMSH6, hPMS1, and hPMS2. Germline mutations in these genes lead to loss of the normal protein encoded by these genes, and tumors that possess these mutations are often referred to as "replication error-positive (RER-positive)" tumors, a condition identified in 12-14% of all cases of colorectal carcinoma. ProPath Immuno-histochemistry Laboratory offers staining using antibodies raised against hMLH1 protein and hMSH2 protein, (encoded by the respective mismatch repair genes), which are normally expressed in the nucleus of cells.



Gene products of the hMLH1 and hMSH2 mismatch repair genes are normally strongly expressed (reflected by nuclear staining) and readily detectable in many normal tissues, such as germinal centers of tonsil (left) and endometrial glands (right).

The absence of nuclear expression of one or both of these proteins has been found to correlate with the presence of a mismatch repair gene defect in the respective gene. Recent studies have found that hereditary non-polyposis colorectal cancer syndrome (HNPCC) (a.k.a. Lynch syndrome, which accounts for 1-5 % of all cases of colon carcinoma) is often caused by germline mutations in one of several mismatch repair genes, as 50-70% patients with HPNCC have been found to have deficient DNA mismatch repair. Germline mutations of the hMLH1 or hMSH2 genes account for 80-90% of mutations found in HNPCC patients.



Immunostains on a colonic adenocarcinoma showing strong nuclear reactivity for the hMSH2 gene product (left), but lack of nuclear staining for the hMLH1 gene product (right). The lack of nuclear staining for hMLH1 has been found to correlate with mutations in that gene, so this tumor would be considered a “replication error-positive” (RER-positive) tumor. This patient and the patient’s relatives should be evaluated for the hereditary non-polyposis colon cancer syndrome.

Patients with HNPCC have an 80-90% lifetime risk of colorectal carcinoma (which may occur as multiple tumors), and typically have an earlier onset (mean age of onset 42, vs. 65 years for conventional colon cancer). The tumors usually occur in the right colon, are not associated with multiple polyps, usually show diploid DNA content, often show prominent mucin production, poor differentiation, a Crohn's-like lymphoid infiltrate, and interestingly have a better prognosis than conventional colon cancer. Some

patients with HNPCC (Lynch Syndrome type II) also have increased risk of other cancers, including carcinomas of endometrium, ovary, breast, small intestine, stomach, pancreas, bile ducts, and urinary tract. Identification of patients with this syndrome is important since genetic analysis of family members can identify those that may carry a defective gene. For this reason, some authors recommend immunohistochemical staining of colon cancer tissue from patients who present at a young age, to attempt to identify the presence of an abnormal DNA mismatch repair gene.

Not all patients with RER-positive tumors demonstrate a positive family history, although study of patients with sporadic RER-positive colorectal carcinomas (that lacked nuclear expression of hMLH1 or hMSH2) showed striking similarities to patients with HNPCC, including frequent location in the proximal colon (although some may present initially in left colon), increased incidence of multiple tumors at presentation, and presentation in a young (< 50) age group. Similar to HNPCC tumors, they had a better prognosis than RER-negative tumors, but showed a poor response to adjuvant chemotherapy. These patients also demonstrated a higher risk of developing additional colorectal carcinomas (5.54 times the risk of RER-negative tumors), suggesting that they may benefit from longer and more vigilant follow-up than patients with RER-negative tumors. Presumably, a subset of these sporadic RER-positive patients probably represent clinically unrecognized cases of HNPCC, and should be investigated for a positive family history.

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Rodney T. Miller, M.D.
Director of Immunohistochemistry
(214) 237-1631
rmiller@propathlab.com