

POSTER PRESENTATION

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Heritable epigenetic mutation of MLH1 in a mother and daughter with Lynch syndrome

Amie M Blanco^{1*}, Yunn-Yi Chen¹, James P Grenert¹, Stephen N Thibodeau², Jonathan P Terdiman¹

From 13th Annual Meeting of the Collaborative Group of the Americas on Inherited Colorectal Cancer Honolulu, Hawaii, USA. 16-17 October 2009

Background

Lynch syndrome is a hereditary predisposition to colorectal and endometrial cancers, in addition to cancers of the stomach, ovary, upper urinary tract, small bowel, hepatobiliary tract, skin and brain. Lynch syndrome is caused by defects in DNA mismatch repair (MMR), and germline mutations in MLH1, MSH2, MSH6 and PMS2 as well as high levels of tumor microsatellite instability (MSI) and loss of MMR protein expression are frequently found. MMR deficiency due to loss of MLH1 in tumor tissue may also be due to gene silencing resulting from hypermethylation of the MLH1 promoter, which is found in 15% of sporadic colorectal and endometrial cancers, and as the second "hit" in some individuals with germline mutations in MLH1. Recently, epigenetic silencing of MLH1 in normal body cells has been proposed as a novel cause of predisposition to Lynch syndrome associated tumors. Twenty five cases of hypermethylation of the MLH1 promoter in peripheral blood (MLH1 epimutation) of individuals with young onset colorectal cancer and/or endometrial cancer have been reported. The heritability of MLH1 epimutation is still under investigation.

Methods and results

A 39-year-old woman from the Philippines was diagnosed with stage III rectal cancer. Her rectal biopsy was screened for evidence of MMR deficiency, which showed high levels of MSI and loss of MLH1 and PMS2 protein expression. Her mother was diagnosed with synchronous colon and endometrial cancers at

age 40. She underwent germline mutation analysis of MLH1 which failed to identify a mutation. Her rectal tumor was screened for MLH1 promoter methylation and BRAF V600E, which showed hypermethylation of the MLH1 promoter in both tumor and normal colonic mucosa, and negative BRAF V600E. Analysis of MLH1 promoter methylation in her peripheral blood was consistent with MLH1 epimutation. Tissue from her mother's colon tumor, endometrial tumor, and normal body tissue showed high levels of MSI, loss of MLH1 protein expression, negative BRAF V600E, and hypermethylation of the MLH1 promoter. Her mother died from her colon cancer in 1995, thus peripheral blood was not available. The patient has two unaffected siblings, ages 31 and 35, who have undergone MLH1 epimutation testing. Neither showed hypermethylation of the MLH1 promoter in peripheral blood.

Conclusions

This case report represents only the third known instance of maternal, transmission of MLH1 epimutation. The first was MLH1 epimutation in an unaffected son of a woman with endometrial, colorectal, and rectal cancers who was found to have MLH1 epimutation. The second was MLH1 epimutation in the 64-year-old unaffected mother of a young woman with colorectal cancer at age 39 and MLH1 epimutation. To our knowledge, our case is unique in that it represents the first case of MLH1 epimutation in a clinically affected mother and daughter, supporting the heritability of MLH1 epimutation as a rare but important cause of Lynch syndrome.

* Correspondence: amie.blanco@ucsfmedctr.org

¹University of California San Francisco, Helen Diller Family Comprehensive Cancer Center and Department of Medicine, San Francisco, California 94115, USA

Author details

¹University of California San Francisco, Helen Diller Family Comprehensive Cancer Center and Department of Medicine, San Francisco, California 94115,

USA. ²Mayo Clinic Departments of Laboratory Medicine and Pathology and Laboratory Genetics, Rochester Minnesota, USA.

Published: 25 May 2010

doi:10.1186/1897-4287-8-S1-P3

Cite this article as: Blanco *et al.*: Heritable epigenetic mutation of MLH1 in a mother and daughter with Lynch syndrome. *Hereditary Cancer in Clinical Practice* 2010 **8**(Suppl 1):P3.

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