

OncoGeneDx: MSH2 Exons 1-7 Inversion Analysis

CLINICAL FEATURES

Approximately 1 in 20 individuals (5%) will develop colorectal cancer in their lifetime (*SEER*). Most cases of colorectal cancer develop sporadically with no family history of the cancer; however, approximately 5% of cases are thought to be due to a hereditary cancer predisposition syndrome. Features suggestive of hereditary cancer predisposition include: young age at diagnosis (before age 50), multiple primary cancers in a single individual, multiple colon polyps, diagnosis of an uncommon cancer type (such as ovarian cancer, ampullary cancer or pancreatic cancer) and several relatives affected with related cancers spanning multiple generations. Lynch syndrome, also known as Hereditary Non-Polyposis Colorectal Cancer syndrome, is reported as the most common hereditary colorectal cancer predisposition syndrome and is estimated to be responsible for 2% of all colorectal cancer diagnoses (Cunningham 2001).

Colon and endometrial cancer are the predominant Lynch syndrome-related cancers that carriers of pathogenic variants are at risk to develop. The lifetime risk of colon cancer has been estimated to be 15%-80% for both male and female pathogenic variant carriers while the lifetime risk for endometrial cancer has been estimated to be 15%-61% for female pathogenic variant carriers. Importantly, cancer risks vary among the mismatch repair genes with some conferring greater cancer risks than others (Bonadona 2011, Baglietto 2010, Senter 2008, Quehenberger 2005, Vasen 1996). In general, the lifetime cancer risks are thought to be lower for those harboring pathogenic *MSH6* and *PMS2* variants compared to those with pathogenic *MLH1*, *MSH2* and *EPCAM* variants. Individuals with Lynch syndrome also have an increased risk of ovarian ($\leq 20\%$), gastric ($\leq 7\%$), urothelial ($\leq 8\%$), small bowel ($\leq 4\%$) and brain cancers ($\leq 3\%$, Turcot variant) (Bonadona 2011, Weissman 2011). Additionally, some individuals with Lynch syndrome also have an increased risk of sebaceous neoplasms and keratoacanthomas of the skin (Muir-Torre variant).

Recently, an inversion of exons 1-7 in the *MSH2* gene was found in a cohort of individuals, who previously tested negative via traditional analyses, with clinical histories and pathological data suggestive of Lynch syndrome (Rhees 2014). Using both multiplex PCR and electrophoresis we are able to detect this inversion giving those who are suspected as having Lynch syndrome an additional testing option.

INHERITANCE PATTERN

Lynch syndrome is inherited in an autosomal dominant manner which requires that an individual carry a single pathogenic *MSH2* variant, or any one of the other four Lynch syndrome-associated genes, to develop symptoms. De novo (new) pathogenic variants in *MSH2* are uncommon; and in this case, the inversion of exons 1-7 in *MSH2* may be a pathogenic founder variant and as such, would likely be inherited from a parent.

Biallelic pathogenic *MSH2* variants, or any of the genes associated with Lynch syndrome, (i.e. one pathogenic variant in each copy of the gene), is associated with an extremely rare autosomal recessive syndrome called constitutional mismatch repair deficiency (*CMMR-D*) syndrome. This disorder is characterized by an increased risk for certain cancers in children, including hematologic malignancies, brain tumors, and colon cancer, as well as multiple adenomatous polyps and café-au-lait macules (Durno 2010, Wimmer 2010). Of note, there is a report of a child with *CMMR-D* who is compound heterozygous for a pathogenic *MSH2* and *EPCAM* variant (Li-Chang 2013). Any individual with a pathogenic *MSH2* variant who is considering pregnancy should be offered reproductive counseling.

TEST METHODS

Using the genomic DNA from the submitted specimen, multiplex PCR was performed to amplify the sequence near the 3' intragenic breakpoint of the *MSH2* Exons 1-7 inversion (Rhees 2014). The PCR fragments are

analyzed by size using electrophoresis and compared to positive and negative controls to determine the presence or absence of the inversion. Confirmation of the *MSH2* Exons 1-7 inversion was performed by a second PCR using a separate DNA preparation if possible. If present, apparently homozygous variants were confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out.

TEST SENSITIVITY

Multiplex PCR and electrophoresis are used to detect the presence or absence of this inversion.

Technical Limitations: False negatives may occur in the setting of bone marrow transplantation, recent blood transfusion, or suboptimal DNA quality. In individuals with active leukemia or lymphoma or with known chronic myeloid or lymphoid neoplasms (such as low grade MDS, CML, ET, P. vera, PMF, CLL), there is a possibility that testing of specimens containing leukocytes may detect an acquired somatic variant, resulting in a false positive result. In this situation, please contact one of our genetic counselors to discuss the utility of submitting an alternate specimen. When testing for a specific variant identified at a laboratory other than GeneDx, rare false negatives may occur if a positive control is not provided. The ability to detect genetic variants and naming conventions can differ among laboratories.

Gene	Protein	Inheritance	Disease Associations
MSH2	dna mismatch repair protein msh2	AD	Lynch syndrome (LS): Colorectal, Endometrial, Ovarian, Gastric, Urinary tract, Pancreatic, Biliary tract, Small bowel & Brain cancer, Sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome

Because of evolving and expanding phenotypes, this list of cancer/tumor types is not exhaustive. Gene-specific risk for some of the cancers and other features listed are not well-defined.

Abbreviations:

AD – Autosomal dominant
AR – Autosomal recessive

CGH – Comparative genomic hybridization
MLPA – Multiplex ligation-dependent probe amplification

REFERENCES

1. Baglietto L et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. J Natl Cancer Inst. 2010 Feb;102(3):193-201. (PMID: 20028993)
2. Bonadona V et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011 Jun;305(22):2304-10. (PMID: 21642682)
3. Canto M et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut. 2013 Mar;62(3):339-47. (PMID: 23135763)
4. Cunningham JM et al. The frequency of hereditary defective mismatch repair in a prospective series of unselected colorectal carcinomas. Am J Hum Genet. 2001 Oct;69(4):780-90. (PMID: 11524701)
5. Durno CA et al. The gastrointestinal phenotype of germline biallelic mismatch repair gene mutations. Am J Gastroenterol. 2010 Nov;105(11):2449-56. (PMID: 20531397)
6. Li-Chang HH et al. Colorectal cancer in a 9-year-old due to combined EPCAM and MSH2 germline mutations: case report of a unique genotype and immunophenotype. J Clin Pathol. 2013 Jul;66(7):631-3. (PMID: 23454724)
7. Quehenberger F et al. Risk of colorectal and endometrial cancer for carriers of mutations of the hMLH1 and hMSH2 gene: correction for ascertainment. J Med Genet. 2005 Jun;42(6):491-6. (PMID: 21642682)
8. Rhee J et al. Inversion of exons 1-7 of the MSH2 gene is a frequent cause of unexplained Lynch syndrome in one local population. Fam Cancer. 2014 Jun;13(2):219-25. (PMID: 24114314)
9. Senter L et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology. 2008 Aug;135(2):419-28. (PMID: 18602922)

10. Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. SEER Cancer Statistics Review, 1975-2012: Lifetime Risk Tables (URL: <http://surveillance.cancer.gov/devcan>) [February 2016 accessed].
11. Vasen HF et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology*. 1996 Apr;110(4):1020-7. (PMID: 8612988)
12. Weissman SM et al. Genetic counseling considerations in the evaluation of families for Lynch syndrome--a review. *J Genet Couns*. 2011 Feb;20(1):5-19. (PMID: 20931355)
13. Wimmer K et al. Constitutional mismatch repair-deficiency syndrome. *Haematologica*. 2010 May; 95(5): 699-701. (PMID: 20442441)