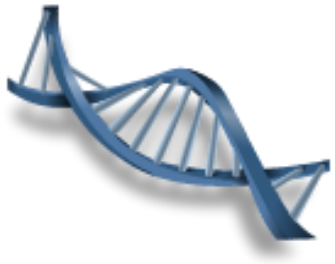

Genetics Corner

Where's my mutation? When patients with Lynch syndrome have no identifiable germline genetic mutation

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Previous articles have discussed Lynch syndrome (LS) and its clinical features. LS is inherited in an autosomal dominant manner and is most commonly associated with cancers of the colon and uterus. This article will provide an overview of how to handle patients who have LS, but have no identifiable genetic germline mutation.

Determining whether someone has Lynch syndrome

The NCCN recommends anyone who meets revised Bethesda guidelines or Amsterdam criteria have immunohistochemistry (IHC) staining and/or microsatellite instability (MSI) testing on their colon and/or endometrial cancers. IHC and MSI testing are used to help determine whether patients have a germline genetic mutation, as it is too costly to test for all of the genetic mutations associated with LS concurrently. IHC and MSI have very similar sensitivities, but IHC results make it possible for clinicians to target specific molecular and/or tumor studies. Having an abnormal IHC result greatly increases the chance that the cancer is hereditary, particularly in the context of a suspicious personal and/or family history. Alternatively, due to the (low) false negative rate of IHC, a strong family history of LS-related cancer overrides a normal IHC result.

The process and interpretation of IHC staining:

IHC staining is used to determine whether MLH1, MSH2, MSH6, and PMS2 proteins expressed by mismatch repair genes are present or absent in cancerous tissue. Having all four stains present is considered a normal result, decreasing the chance of having a hereditary form of cancer. The pattern of loss of IHC staining is used to determine which LS-related genes would be the best to test for in peripheral blood.

Take for example a patient whose IHC result shows loss of staining of MLH1 and PMS2. For patients who are younger than 50, MLH1 molecular testing (via peripheral blood) is ordered first. If negative, BRAF (V600E) testing and MLH1 promoter hypermethylation studies on the tumor may be ordered to confirm that the MLH1 absence in the tumor is due to a somatic (not hereditary) event only. Tumors that test positive for BRAF V600E mutation or MLH1 hypermethylation are not due to LS.

In patients over 50, tumor testing for BRAF V600E and MLH1 hypermethylation studies may be ordered before MLH1 germline (peripheral blood) sequencing. A mutation found in MLH1 indicates the patient has LS. Other IHC staining results suggest testing of the genes MSH2, MSH6, PMS2, and/or EPCAM. These genes are associated with hereditary form of colon and/or endometrial cancer.

We expect to find genetic mutations in many individuals whose tumors show an abnormal IHC result. However, the inability to find a germline mutation in patients whose LS-related tumor show reduced expression of MLH1, MSH2, MSH6, and/or PMS2 is becoming

more common. Interestingly, our internal data from LS patients at Parkland show that 50% have clinical diagnosis of LS without a detectable germline mutation.

When germline genetic mutations cannot be found, do they have LS:

Patients who have colon/endometrial tumors exhibiting absent staining on IHC as previously described (and, if applicable, negative BRAF and MLH1 hypermethylation, and high microsatellite instability with other LS-associated tumor pathology) have LS, regardless of whether a germline genetic mutation can be found. Also, patients with a family history that meets Amsterdam II criteria have LS, regardless of whether a mutation can be identified. When a mutation cannot be found in the patient, it is not possible to tell whether unaffected family members have LS. In these situations, a personalized screening regimen based on family history should be put in place for all family members (NCCN, 2011). Until further research identifies more LS mutations, all family members of patients with LS should speak with their health care providers about a personalized screening regimen consistent with LS.

Cancer risk and screening options for individuals with LS:

Patients with LS are considered to be at high risk for colon and endometrial cancer. They also have an increased risk for cancers of the stomach, ovary, urinary tract, small bowel, brain/CNS, pancreas, liver, and specific skin tumors (Weissman et al. 2011). Recent evidence suggests an association between LS and breast cancer (Walsh et al. 2010). Experts have proposed management guidelines for patients with LS. A summary of guidelines by NCCN 2011 are as follows:

-Colonoscopies every 1-2 years beginning between 20-25 years of age (or earlier depending on family history).

-Annual screening for endometrial and ovarian cancer can be considered between 30 and 35 years of age and then consider risk-reducing total hysterectomy bilateral salpingo-oophorectomy (TAHBSO) after childbearing is complete.

-An upper endoscopy with extended duodenoscopy beginning at 30-35 every 2-3 years – capsule endoscopy can be considered at the same intervals, particularly in families with higher prevalence of small bowel cancers.

-Consider annual urinalysis with cytology at LS diagnosis.

-Annual physical and history update (Weissman et al. 2011).

If patients do not need an identifiable LS mutation to have LS, why bother doing germline genetic testing?

Identifying a patient's mutation makes it possible to determine whether other family members have LS. This is particularly useful for family members who have not yet been diagnosed with a LS-related cancer, and therefore may not be monitored appropriately. Once a patient's germline mutation has been identified, testing other family members for the same mutation is an option. Any first-degree relative of the patient has a 50% chance of having inherited the same mutation. Generally, first-degree relatives are tested first to determine other more distant relatives that may be at risk. Family members who test positive for the familial mutation have LS and should adhere to LS management guidelines. Family members who test negative for the familial mutation are considered to be at population risk for the cancers listed above and do not require increased surveillance.

As always, please contact your friendly genetic counselor with questions at 817-838-4874.

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