A case of *de novo* Lynch syndrome with germline mosaicism

The James

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BACKGROUND

- *De novo* mutations in the mismatch repair (MMR) genes are uncommon and have been reported to occur at a rate of 5.1% in population-based mutation carriers.[1]
- Germline mosaicism is less common, occurring with varying frequency among autosomal dominant disorders, with higher rates in genes with higher *de novo* mutation rates.
- Here, we present the case of a 36-year-old Serbian male diagnosed with colorectal cancer who had no known family history of cancer and was found to have an *MLH1* mutation as a result of germline mosaicism.

SUMMARY OF TESTING-PROBAND

Immunohistochemistry on Colon Tumor

MLH1, MSH2, MSH6 intact	**PMS2 weakly expressed***

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Immunohistochemistry and microsatellite instability testing performed at a second lab

MSI-H	**MSH2 & MSH6 intact**	**MLH1 absent, PMS2 weakly expressed***

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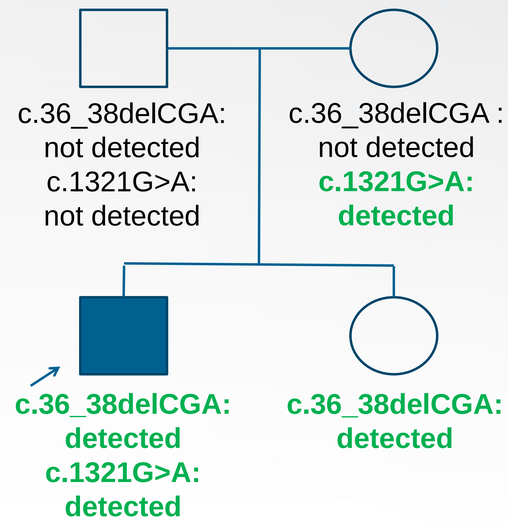
***MLH1* and *PMS2* Sequencing and MLPA**

***MLH1*: two variants of unknown significance: c.36_38delCGA and c.1321G>A (p.A441T)**	***PMS2*: Negative, no mutations detected**

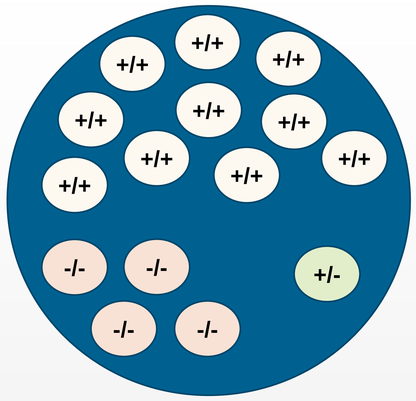
* A potential explanation for the differing IHC results is that the two labs used different MLH1 antibodies.

MLH1 SINGLE SITE ANALYSIS - PARENTS AND SISTER



- **Parental Testing (Single site analysis):**
  - c.1321G>A was inherited from his mother
  - c.36_38delCGA was absent in both parents
- **Reclassification of c.36_38delCGA as pathogenic due to:**
  - *De novo* mutations in cancer patients with MSI-high tumors are likely to be pathogenic given the low rate of *de novo* mutations in the general public and this was confirmed by the International Society for Gastrointestinal Hereditary Tumours (InSiGHT).[2]
  - InSiGHT had reclassified the c.1321G>A alteration as benign.
- **Proband's 26-year-old sister's testing** (analysis of c.36_38delCGA):
  - Offered due to the rare possibility of maternal germline mosaicism
  - Positive for the c.36_38delCGA mutation in *MLH1*

TA-CLONING



- Results from TA-cloning indicated that the **odds are >93% that the alterations are *in cis***, with c.36_36delCGA occurring on the **maternal** allele:
  - 10 of 15 colonies had both alterations
  - 1 of 15 colonies had only the c.1321G>A alteration
  - 4 of 15 colonies had neither alteration
- In combination with the results from family testing, this suggests maternal germline mosaicism for c.36_36delCGA.

MLH1 NEXT GENERATION SEQUENCE ANALYSIS - MOTHER

- To assess for low level mosaicism of c.36_38delCGA in the maternal blood, *MLH1* analysis was repeated using next generation sequencing.
  - Results did not demonstrate low-level mosaicism (forward and reverse directions shown in top and bottom images, respectively).
- Testing is in progress to assess for somatic mosaicism in the mother's ovarian and cervical tissue.

TAKE HOME POINTS

1. This patient has an apparently *de novo MLH1* mutation which originated from germline mosaicism in his mother.
2. Clinical management of the proband and his sister who have the mutation in their germline is clear; however, management of the mother is unclear at this time.
3. This case demonstrates that some Lynch syndrome patients will not have a family history of cancer.

REFERENCES

1. Win et al. J Med Genet. 2011 Aug;48(8):530-4.
2. InSiGHT; [database on the Internet]. Available from: http://insight-group.org.

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