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

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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. Germline mosaicism is less common, occurring with varying frequency among autosomal dominant disorders, with higher rates in genes with higher *de novo* mutation rates.
Methods: A 36-year-old Serbian male with no family history of cancer was diagnosed with colorectal cancer and underwent universal tumor screening at our institution. Immunohistochemistry (IHC) indicated that the MLH1, MSH2, and MSH6 proteins were intact, but the PMS2 protein was weakly expressed. Genetic counseling was provided and microsatellite instability (MSI) testing was ordered to determine whether defective MMR might be due to weak PMS2 expression. In addition, IHC was repeated at a second lab.
Results: Additional tumor study results showed the tumor was MSI-high and confirmed that PMS2 expression was weak; however, the second lab also reported loss of the MLH1 protein. A potential explanation for the differing IHC results is that the two labs used different MLH1 antibodies. Sequencing and MLPA of the *MLH1* and *PMS2* genes revealed *two* variants of uncertain significance in the *MLH1* gene; c.36_38delCGA and c.1321G>A, encoding p.A441T. Site-specific testing of his parents indicated that the c.1321G>A alteration was inherited from his mother and neither parent carried the c.36_38delCGA alteration. 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 the c.36_38delCGA and the c.1321G>A mutation; 1 of 15 colonies had only the c.1321G>A mutation; and 4 of 15 colonies had neither mutation). The testing laboratory subsequently reclassified the c.36_38delCGA alteration as pathogenic based on data that *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; v1.9: 5/09/2013). In addition, InSiGHT had reclassified the c.1321G>A alteration as benign. Therefore, predictive testing was offered to the proband's 26-year-old sister, due to the rare possibility that their mother had germline mosaicism for the apparently *de novo* mutation. The proband's sister tested positive for the c.36_38delCGA mutation in *MLH1*.
Conclusions: This patient has an apparently *de novo MLH1* mutation which originated from germline mosaicism in his mother. It is not yet known whether the mother also has somatic mosaicism for this mutation. The proband's mother is being retested by next-generation sequencing to assess for low-level somatic mosaicism detectable in other tissues. 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. This case demonstrates that some Lynch syndrome patients will not have a family history of cancer.