MSH2 inversion phenotype is similar to other *MSH2* mutations

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Background: Lynch syndrome (LS) is a well described hereditary cancer syndrome caused by mutations in the mismatch repair (MMR) genes (*MLH1, MSH2, MHS6, PMS2*) and *EPCAM*. Many sequence based mutations and large rearrangements have been reported in the *MSH2* gene and the phenotype of these mutation carriers is well understood. While the range of cancer risks for individuals with LS varies for the different genes, individuals with *MSH2* mutations have high risks for colorectal (CRC), endometrial, and other cancers and are more likely to have sebaceous neoplasms than those with mutations in other LS genes. An inversion of *MSH2* exons 1-7 has been reported in a small number of individuals with LS and commercial testing for this inversion recently became available. We aimed to describe the genetic test(s) ordered for, and clinical phenotype of, individuals assessed for this *MSH2* inversion in our laboratory between November, 2014 and June, 2015.
Methods: The *MSH2* inversion of exons 1-7 was detected using a two PCR strategy followed by agarose gel electrophoresis. The inversion was automatically included in all *MSH2* sequencing orders, included by request with panels, or ordered individually. Clinical history data were gathered retrospectively from information submitted on and with test request forms.
Results: Of 587 probands tested, nine (1.5%) were positive for the *MSH2* inversion, and all nine had a personal and/or family history of LS associated cancers. One of the nine was tested only for the inversion due to previous negative *MSH2, MSH6,* and *EPCAM* testing in an affected first degree relative. The remaining eight had additional previous or concurrent testing. Four family members of the probands tested positive for the inversion and were included in the phenotypic assessment. Nine of the 13 positive individuals had a personal history of cancer, eight probands and one family member. Eight of nine affected individuals had at least one CRC diagnosis and five had two or more LS associated cancers. The only individual without CRC had a personal history of sebaceous carcinoma and family history of LS associated cancers. The only proband without cancer had a history of sebaceous adenomas and a family history of early onset CRC. Results of immunohistochemistry (IHC) for the MMR proteins were available for seven of nine affected cases and the individual with sebaceous adenomas: seven reported loss of MSH2 and MSH6, and one individual with cancer reported loss of MSH2 only. Interestingly, all positive probands had Caucasian (90%) or mixed Caucasian and other (10%) ethnicity while only 61% and 1% of all tested probands had Caucasian and mixed Caucasian ethnicity, respectively.
Conclusions: The results of this analysis suggest that individuals with the *MSH2* inversion of exons 1-7 have a similar phenotype to those with other mutations in *MSH2*, including cancer history and IHC results; however, the inversion may be more common in those with Caucasian ethnicity. This is the largest reported cohort tested for the *MSH2* inversion to date, but it is a biased cohort as many individuals were highly suspicious for LS and negative for previous testing, possibly explaining the high positive rate (1.5%). Collectively, these data suggest that all individuals suspicious for a mutation in *MSH2* should have analysis for this inversion. Larger studies are needed to further define the phenotype, frequency, and any associated ethnicity of individuals with the *MSH2* inversion of exons 1-7.