MISMATCH REPAIR DEFICIENT TUMORS LACKING KNOWN SPORADIC CAUSES: ARE THEY ALL DUE TO LYNCH SYNDROME?


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BACKGROUND: Mismatch repair deficient (MMRD) colorectal (CRC) or endometrial (EC) cancers in the absence of MLH1 promoter hypermethylation and BRAF mutations are suggestive of Lynch syndrome (LS). Positive germline genetic test results confirm LS. It is unclear if individuals with MMRD tumors but no identified germline mutation or sporadic cause (MMRD+/germline-) have LS.

HYPOTHESIS: Since LS is hereditary, individuals with LS should have a stronger family history of LS-related cancers than individuals with sporadic tumors. We hypothesized that MMRD+/germline- CRC and/or EC patients would have less suggestive family histories than LS CRC and/or EC patients.

METHODS: 253 individuals with an MMRD CRC or EC who underwent genetic counseling at one institution were included in analysis in 1 of 4 groups: LS, MMRD+/germline-, MMRD+/VUS, sporadic MSI-H (MMRD tumor with MLH1 promoter hypermethylation or BRAF mutation). Family histories were analyzed utilizing MMRpro and PREMM1,2,6. Kruskal-Wallis tests were used to compare family history scores. Logistic regression was used to determine what factors were predictive of LS.

RESULTS: MMRD+/germline- individuals had significantly lower median family history scores (PREMM1,2,6=7.3, MMRpro=8.1) than LS individuals (PREMM1,2,6=26.1, MMRpro=89.8, p<0.0001); and had significantly higher median family history scores than sporadic MSI-H (PREMM1,2,6 =5.0,
p=0.0013, MMRpro=0.7, p<0.0001). Family history scores were positively correlated with likelihood of testing germline positive (p<0.0001).

CONCLUSION: MMRD+/germline- individuals have less suggestive family histories of LS than LS individuals, but more suggestive family histories than sporadic MSI-H individuals. CRC and/or EC patients with abnormal tumor studies are more likely to have a germline LS mutation if they have a family history suggestive of hereditary cancer. These results imply that the MMRD+/germline- group may not all have LS. This finding highlights the need to determine other somatic, epigenetic or germline causes of MMRD tumors so that these patients can be accurately counseled regarding screening and management.