Unknown Synergistic Effect of Digenetic Inheritance of MMR Pathogenic Mutations: Double Heterozygosity in Lynch Syndrome, A Single Case Report & Family Study

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Background: Lynch syndrome (LS) is a well-known cause of hereditary colon cancer. Pathogenic and likely pathogenic variants ("mutations") in mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6* and *PMS2* along with deletions of *EPCAM* have been associated with LS. Biallelic mutations in MMR genes result in constitutional mismatch repair deficiency (CMMR-D) syndrome. Current understanding of double heterozygosity for MMR mutations is that it does not cause CMMR-D syndrome, but is expected to be associated with cancer risks similar to LS.

A 22-year-old male presented to our clinic with a diagnosis of locally advanced rectal adenocarcinoma. The tumor demonstrated microsatellite instability and loss of MLH-1, MSH-6, and PMS-2 expression with retention of MSH-2 by immunohistochemistry. His family history was significant for endometrial cancer in his paternal grandmother diagnosed at age 52. The remaining family history was non-contributory. The patient underwent multigene panel testing. The patient was found to be heterozygous for a mutation in the *MSH6* gene (p.R482*) and a mutation in the *PMS2* gene (EX6_8del). The patient's nuclear family members underwent genetic testing to determine the segregation of the familial mutations and to better clarify their personal cancer risks. We confirmed the *MSH6* mutation was paternally inherited and the *PMS2* mutation was maternally inherited. The patient's oldest sister is heterozygous for the *PMS2* mutation, his younger brother is also heterozygous for the *PMS2* mutation, and his adolescent sister is a double heterozygote.

Methods: Genetic test results were reviewed for individuals who were tested for two or more MMR genes from a single clinical diagnostic laboratory between July 2009 and March 2016. Medical and family histories obtained from test requisition forms were reviewed to assess the clinical outcome of LS double heterozygotes.

Results: In a cohort of over 75,000 cases tested for two or more MMR genes at a clinical diagnostic laboratory, seven double heterozygotes from six families were identified (0.009%). Six out of the seven individuals had a diagnosis of at least one LS-related cancer; the remaining individual had a diagnosis of breast cancer. All seven individuals had first-degree or second-degree relatives with colorectal or endometrial cancer.

Conclusions: There are few case reports of LS double heterozygotes published in the literature. Due to this rarity, the interactive effect of harboring mutations in two different MMR genes is unknown and the relative cancer risk cannot be predicted. Further studies are needed exploring the functional impact of double heterozygous MMR mutations to help clarify lifetime cancer risks and appropriate management for these patients.

Tentative Presentation: The 2016 NSGC 35th Annual Education Conference in Seattle, WA.