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**Abstract 1285: Identification of MMR gene exonic rearrangements in suspected Lynch syndrome tumors without loss of MMR expression**

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**Abstract**

Lynch syndrome (LS), also called Hereditary Non-Polyposis Colorectal Cancer, the most well studied form of familial CRC, is responsible for about 3% of all CRC cases. LS-associated CRC often exhibits one or more of the following features namely early age of onset, occurrence of synchronous/metachronous tumors, presence of more than one affected family member and tumors predominantly localized to the proximal/right colon with specific clinico-pathological features such as a mucinous histology, poor differentiation and immune infiltration. LS is primarily a disease of defective MisMatch Repair (MMR) and is caused by germline mutational inactivation of any one of four major MMR genes viz. MLH1, MSH2, MSH6 and PMS2. A hallmark of LS-associated tumors is presence of ‘microsatellite instability’ (MSI), a term used to describe frequent occurrence of expanded/contracted microsatellites that arise during DNA replication and are not corrected due to defective MMR. MLH1 and MSH2 account for a majority (up to 90%) of LS cases while MSH6 and PMS2 are involved in a minor proportion. Mutational inactivation of an MMR gene almost always results in loss of corresponding protein expression in the tumor, which can be easily detected by immunohistochemistry. In the first comprehensive study from India, we analyzed MSI and determined expression status of the four MMR genes in forty eight suspected LS-associated colorectal tumor samples. Though a majority (85.4%) exhibited MSI, only 58% exhibited loss of MMR expression, a significantly low proportion compared to reports from other populations. PCR-DNA sequencing and Multiple Ligation-dependent Probe Amplification based mutation and exonic deletion/duplication screening respectively, revealed MMR gene lesions in 81% of samples exhibiting loss of corresponding MMR protein expression, including thirteen mutations and four exonic rearrangements. Seven novel mutations (four in MLH1 and three in MSH2) were identified. Surprisingly, MMR gene lesions were also detected in a significant proportion (78%) of tumor samples not exhibiting MMR expression loss. Interestingly, samples with and without MMR expression exhibited significant differences with respect to mucinous histology and instability exhibited by specific microsatellites. In addition, MMR negative samples mainly harbored MMR gene in-del or point mutations while MMR positive samples predominantly harbored MMR gene exonic rearrangements. The study has therefore revealed for the first time a significant proportion of suspected LS tumors not exhibiting loss of MMR expression despite harboring MMR gene rearrangements. More importantly, our results indicate significant differences in the biology of LS-associated colorectal tumors occurring due to missense/in-del mutations in MMR genes causing loss of expression and those that occur due to MMR gene exonic rearrangements not resulting in loss of expression.

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