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LETTER TO THE EDITOR

New genetic variants of genes MMR in a Spanish family with Lynch syndrome

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Dear Editor:

Lynch syndrome is an autosomal dominant inheritance and the most hereditary form of colorectal cancer [1]. The identification of the molecular genetic basis of Lynch syndrome enabled the implementation of predictive testing in families with a proven mutation. A prerequisite to detect patients with Lynch syndrome is the knowledge of the clinical and histopathological features of this disease [2]. The molecular genetics underlying mechanism is a mutation in one of the mismatch–repair genes (most commonly MLH1, MSH2, and MSH6), that has added significantly important information to the recognition of this disease and the search for high-risk individuals as well as offering them a genetic counseling. We report a rare mutation in gene MLH1 (117-1 G>K) in nine members of a family, some of them with undetected Lynch syndrome. The genetic analysis were performed to confirm or to detect possible predisposition to hereditary nonpolyposis colorectal cancer (HNPCC). Six members of this family case present the single mutation in MLH1 117-1 G>K and some of them were confirmed by the doctor to be affected by Lynch syndrome. However, there are no other confirmed results of the pathogenicity effect of this mutation. There are many human online databases where the mutations in different syndromes could be included, such as www. ensembl.org, http://www.ncbi.nlm.nih.gov/gene, and www.hgmd.cf.ac.uk/. And even exclusive database for gastrointestinal hereditary tumors such as http://www.insight-group.org/meetings/MMR/. However, none of them described or included the variants analyzed in the present case report.

The case analysis started in a 59-year-old woman who had been diagnosed with HNPCC and fulfilled the Bethesda and Amsterdam Criteria. She was also confirmed by genetic analysis of mismatch repair (MMR) genes (MLH1, MSH2, and MSH6) by describing mutations in these genes such as 211+9 C>G in MSH2, 3,438+14 A>T in MSH6 and three others in MLH1 being one of them 117-1 G>K mutation. Due to the accelerated carcinogenesis of colorectal cancer (CRC) full colonoscopies are recommended but there are also others options such as the searching of germline mutation carriers. The discovery of mismatch repair germline mutations has improved the search for high-risk individuals throughout families who, with genetic counseling, may become candidates for germline mutation testing [1]. For these reasons, others members of this family (direct relatives and in different generations) has been analyzed in MMR genes, two more sisters 68 and 62 years old, both of them with only 117-1 G>K mutation and later clinically confirmed of Lynch syndrome. One of them, was also affected by endometrial cancer. They also had a death father of CRC and another sister affected by this syndrome.

Their descendents were also studied in MMR genes with 28, 30, 31, and 40 years old, all without symptoms of Lynch syndrome but with a direct relative affected by CRC or endometrial cancer. After the genetic analysis, it was confirmed that all of them have 117-1 G>K mutation, but only this mutation. Others family members were also included to genetic analysis such as two cousins without previous symptoms of CRC, but one of them with endometrial cancer and a mother and a sister affected by this same cancer. All of them have the 117-1 G>K mutation.

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After this genetic analysis, unaffected members of the family are classified as high-risk and they will follow frequent clinical examination for CRC.

In conclusion, our report on a family members with Lynch syndrome and the presence of the polymorphism 117-1 G>K in MLH1 that till the moment is unclassified as pathogenic, could be suggested to have a pathogenic effect by the presence in many family members, some of them affected by this syndrome. This mutation could be suggested in the framework of genetic counseling as pathogenic with the combination of other clinical parameters evaluated as Amsterdam I and II criteria as well as with the revised Bethesda criteria. This mutation and the screening in MMR genes could encourage to individuals in families with pathogenic variants to participate in an intensified screening program. Nowadays, due to the incomplete penetrance of these mutations in MMR genes, there is no recommendation towards prophylactic surgery in high-risk individuals without tumor manifestation. Nevertheless, the effect on quality of life of prophylactic, extended surgery in addition to the obligatory oncologic resection with or without prophylactic hysterectomy needs to be established in prospective controlled trials [2]. With this report, we would like to suggest that molecular genetics biomarkers can be useful tools in identifying subjects at risk of developing cancer and screening for early cancers, so having and updated information of the main polymorphisms in MMR genes is necessary.

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