

# Rare single-nucleotide variants of MLH1 and MSH2 genes in patients with Lynch syndrome

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## Abstract

Approximately 5% of colorectal cancers (CRCs) are hereditary. Lynch syndrome (LS), also known as hereditary nonpolyposis colorectal cancer (HNPCC), is the most common form of recognized hereditary CRC. Although Iran, a developing country, has a high incidence of CRC, the spectrum of mutations has yet to be thoroughly investigated. Therefore, this study aimed to investigate pathogenic and non-pathogenic variants in MLH1 and MSH2 genes in Iranian patients with suspected Lynch syndrome (sLS). In the present study, 25 peripheral blood samples were collected from patients with sLS and high microsatellite instability (MSI-H). After DNA extraction, all samples underwent polymerase chain reaction (PCR) and Sanger sequencing to identify the variants in the exons of MLH1 and MSH2 genes. The identified variants were interpreted using prediction tools, including SIFT, CADD, PolyPhen, PROVEAN, REVEL, MetaLR, and Mutational Assessor. In our study population, 13 variants were found in the MLH1 gene and 8 in the MSH2 gene. Interestingly, 7 of the 13 MLH1 variants and 3 of the 8 MSH2 variants were novel, whereas the remaining variants were previously reported or available in databases. In addition, some patients with sLS did not have variants in the exons of the MLH1 and MSH2 genes. The variants detected in the MLH1 and MSH2 genes had specific characteristics regarding the number, area of occurrence, and their relationship with demographic and clinicopathologic features. We identified two novel pathogenic/likely pathogenic variants in these two genes. Overall, our results suggest that analysis of MLH1 and MSH2 genes alone is insufficient in the Iranian population, and more comprehensive tests are recommended for detecting LS.

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