



Molecular analysis of *MLH1* variants in Chinese sporadic colorectal cancer patients

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Genet. Mol. Res. 15 (2): gmr.15027689

Received September 22, 2015

Accepted December 14, 2015

Published April 25, 2016

DOI <http://dx.doi.org/10.4238/gmr.15027689>

ABSTRACT. Single nucleotide polymorphisms (SNPs) in mismatch repair genes, especially in the *MLH1* gene, are closely associated with susceptibility to hereditary nonpolyposis colorectal cancer. However, few relevant findings are available regarding the association between sporadic colorectal cancer (SCRC) and SNPs of *MLH1* in Chinese patients. Therefore, the present study aimed to describe the pathogenic association between three important *MLH1* polymorphisms and SCRC in the Chinese population. Peripheral blood samples from 156 SCRC patients and 311 healthy controls were collected. DNA was

purified from peripheral blood, and the V384D, R217C, and I219V polymorphisms were evaluated using high-resolution melting analysis and direct sequencing. The association between the three important *MLH1* polymorphisms and clinical pathological features of the SCRC patients was analyzed. In addition, PMS2-*MLH1* protein interactions were determined by co-immunoprecipitation (Co-IP) to determine the protein functional alteration induced by these SNPs. Among the three polymorphisms, V384D was significantly associated with the risk of SCRC (OR = 31.36, $P < 0.0001$). The allele frequencies were 4.81 and 0.16% in the SCRC group. No association was found between SCRC and R217C, or between SCRC and I219V. Moreover, the allele frequency of R217C was significantly higher in the SCRC patients younger than 60 years than in those older than 60 years. Co-IP showed that the *MLH1* R217C, V384D, and I219V variants had relative binding abilities with PMS2 of 0.59, 0.70, and 0.80, respectively, compared with the wild-type. These findings suggest that *MLH1* V384D could be a promising genetic marker for susceptibility to SCRC.

Key words: Single nucleotide polymorphism; Colorectal cancer; High-resolution melting; Mismatch repair gene