Advances in Modern Oncology Research

doi: 10.18282/amor.v3.i3.237

EDITORIAL

Significance of defining a pathogenic variant in hereditary cancer syndrome

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***Keywords*:** Lynch syndrome; ClinVar; pedigree analysis; endometrial cancer; *MLH1* gene variants

***Citation*:** Wong KK. Significance of defining a pathogenic variant in hereditary cancer syndrome. Adv Mod Oncol Res 2017; 3(3): 89–90. http://dx.doi.org/10.18282/amor.v3.i3.237.

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Received: 13th June 2017; **Published Online**: 28th June 2017

With the advances in cancer genetics, over 200 hereditary cancer susceptibility syndromes have been described[1,2]. About 5%–10% of all cancers are caused by hereditary mutations. The most common syndromes are those associated with breast, ovarian and gastrointestinal cancers. The hereditary pattern of stomach and endometrial cancer was first reported by Warthin in 1931[3]. In 1966, Lynch and colleagues reported studies of two extended pedigrees with a similar hereditary pattern of multiple carcinomas and this was designated a cancer family syndrome[4]. This condition was subsequently called hereditary nonpolyposis colorectal cancer (HNPCC). However, the term "Lynch syndrome" has been commonly used to describe this condition since 1984[5].

Lynch syndrome is characterized by inherited mutations of DNA mismatch repair (MMR) genes *MSH2* (MutL homolog 1), *MLH1* (MutS homolog 2), *MSH6* (MutS homolog 6), and *PMS2* (postmeiotic segregation 2) with incomplete penetrance. Not all mutation carriers will develop cancers. For patients with Lynch syndrome, *MLH1* or *MSH2* mutations account for approximately 90% of the germline heterozygous mutations. For women with dual primary cancers, 49% had a colon cancer diagnosed first, while 51% had an endometrial or ovarian cancer diagnosed first.[6] In this issue, Dr. Feng and her group reported a germline mutation in the *MLH1* gene (c.1145dupA) in a 45-year-old woman with atypical endometrial hyperplasia and a colon cancer history at the age of 30. Pedigree analysis of the patient's nine family members provided clinical evidence to support the pathogenic role of the identified *MLH1* gene variant in Lynch syndrome[7].

There are 1,792 *MLH1* gene variants reported in the ClinVar database; however, 692 variants are designated as variants of uncertain clinical significance. ClinVar is a public database that collects reports of human variation and observed health status of patients from both clinical service laboratories and research laboratories[8]. The precise interpretation of gene variant is essential for implementing personalized medicine. The American College of Medical Genetics and Genomics (ACMG) has recommended the use of specific standard terminology – "pathogenic", "likely pathogenic", "uncertain significance", "likely benign", and "benign" – to describe variants identified in genes that cause Mendelian disorders[9]. The use of pedigree analysis and the demonstration of the loss of MLH1 protein expression associated with a variant are essential to designate the *MLH1* gene variant as "pathogenic".

Universal screening for Lynch syndrome among patients with endometrial cancer or colorectal cancer has been proposed[10,11]. To enhance the early diagnosis of individuals with Lynch syndrome, cascade testing for pathogenic variants among the at-risk relatives of those diagnosed with

Lynch syndrome will be crucial[12]. For female mutation carriers of pathogenic variants, prophylactic surgery for the uterus and its adnexa is an option. Aspirin is actively being investigated as a chemoprevention agent for colorectal cancer for patients with Lynch syndrome[13]. Dendritic cell vaccination in patients with Lynch syndrome is also being tested as a preventive measure for persons who are known to be carriers of a germline MMR-gene mutation but with no signs of disease yet (ClinicalTrials.gov Identifier: NCT01885702). Since many mutation variants are still of uncertain clinical significance, and not all mutations are pathogenic, defining the pathogenic nature of mutation variants will be critically important for patient management.

Conflict of interest

The author declares no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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doi:10.18282/amor.v3.i3.237