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Familial Colorectal Cancer Type X (FCCTX) and the correlation with various genes—A systematic review

Mahdieh Nejadtaghi, MSc[a], Hamideh Jafari, MSc[a], Effat Farrokhi, PhD[a,*], Keihan Ghatreh Samani, PhD[b]

[a]Cellular and Molecular Research Center, Shahrekord University of Medical Science, Shahrekord, Iran
[b]Clinical Biochemistry Research Center, Shahrekord University of Medical Science, Shahrekord, Iran

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ABSTRACT

Familial Colorectal Cancer Type X (FCCTX) is a type of hereditary nonpolyposis colorectal cancer in accordance to Amsterdam criteria-1 for Lynch syndrome, with no related mutation in mismatch repair gene. FCCTX is microsatellite stable and is accounted for 40% of families with Amsterdam criteria-1 with a high age of onset. Thus, the carcinogenesis of FCCTX is different compared to Lynch syndrome. In addition to the microsatellite stability and the presence of less predominant tumors in proximal colon, various clinical features have also been associated with FCCTX in comparison with Lynch syndrome such as no increased risk of extracolonic cancers, older age of diagnosis and higher adenoma/carcinoma rate. Genetic etiology of this type of cancer which is autosomal dominant is unknown. In this review, we focus on the genes and their variants identified in this type of CRC. In order to find out the correlation between FCCTX and various genes database such as PubMed and PMC, search engine such as Google scholar and portals such as Springer and Elsevier have been searched. Based on our literature search, several studies suggest that FCCTX is a heterogeneous type of disease with different genetic variants. Recent studies describe the correlation between FCCTX and genes

*Correspondence to: Effat Farrokhi, Cellular and Molecular Research Center, Shahrekord University of Medical Sciences, Rahmatieh, Shahrekord, Iran.
E-mail address: e_farrokhi_k@yahoo.com (E. Farrokhi).

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such as *BRCA2*, *SEMA4*, *NTS*, *RASSF9*, *GALNT12*, *KRAS*, *BRAF*, *APC*, *BMPR1A*, and *RPS20*. Considering the fact that *BRCA2* has the highest mutation rate (60%) and is one of the most crucial DNA repair genes, it will be considered as a big role player in this type of cancer in comparison with other genes.

Introduction

Among patients with clinical characteristics of hereditary nonpolyposis colorectal cancers (CRCs), there is a group known as Familial Colorectal Cancer Type X (FCCTX)[1] which is defined based on Amsterdam Criteria-1 (AC1) for Lynch syndrome.[2] Among this type of CRCs, 40% of families met AC1 criteria.[3] Since this type of cancer has no mutation in mismatch repair gene (MMR), the tumors have been characterized as microsatellite stable.[4] Thus, the carcinogenesis of FCCTX is different compared to Lynch syndrome.[5,6]

In addition to the microsatellite stability and the presence of less predominant tumors in proximal colon, various clinical features have also been associated with FCCTX in comparison with Lynch syndrome such as no increased risk of extra-colonic cancers, older age of diagnosis, and higher adenoma/carcinoma rate.[3,7-9] Despite the recent progress in clinical detection of FCCTX, its genetic etiology has remained unknown.[3] FCCTX may be resulted from more than one genetic etiology.[2] Different studies suggest that FCCTX is a heterogeneous disease with various clinical variants.[10] Detection of the genes associated with FCCTX will facilitate the molecular diagnosis of the disease.[4,9,11] Current evidence shows that FCCTX families constitute a high heterogeneous group. In this review, we focus on the genes and their variants identified in this type of CRC.

The literature review has been performed in order to find out the correlation between FCCTX and various genes. Only studies published in English were included. Keywords such as “FCCTX” and “genes” have been used to search for all articles related to genetic basis of FCCTX.

In this review, we have searched the most recent published articles. Retrieved articles had original contributions or were review articles.

For each study, the following action was performed: collecting information about the numbers of cases and controls, the genes involved, type of mutations, mutation frequency rate, and the type of analyzing process (for instance, linkage analysis or any other studies).The important inclusion factor was fulfilling Amsterdam criteria. Then all related articles were collected, the results were analyzed and a comparison was made between various genes.

Genes

BRCA2 gene

BRCA2 gene has high tumor heterogeneity and it is a good candidate for FCCTX.[12] Some studies show the relation between rare *BRCA2* alleles and CRC[13] and the linkage between a marker in *BRCA2* gene and familial colorectal families.[14] In addition, in recent studies on 48 FCCTX families, 27 coding sequences and intron/exon boundaries in *BRCA2* gene were analyzed and 29 *BRCA2* variants including 28 point mutations (14 missense, 12 silent, and 2 intronic) and 1 frameshift mutation were found. The most striking result of this work was the frameshift mutation c.3847_3848delGT p. (Val1283Lysfs*2) detected in 1 FCCTX family. In this family, 1 breast cancer, 4 CRCs, and 1 prostate cancer in 2 following generations have been found.[12] Val1283Lysfs*2 mutation is reported in the Breast Cancer Information Core database as pathogenic mutation for Hereditary Breast and Ovarian Cancer Syndrome (HBOC) and it has also been observed in prostate cancer.[15]