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Editorial

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MEFV Gene Mutations and Pathologic Gene Polymorphism in Cases with Inflammatory Bowel Diseases

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1. Editorial

1.1. The Genetic Characteristics of Inflammatory Bowel Diseases and Familial Mediterranean Fever

Inflammatory bowel diseases (IBD) are chronic, repetitive diseases caused by regulation defects of the mucosal immune response, which increases against the bacterial antigens in the bowel lumen of patients with genetic susceptibility [1].

In 2001 it was determined that NOD/Caspase recruitment domain (CARD) 15 is a Crohn's Disease (CD) gene localized on chromosome 16 and encodes the NOD2/CARD15 protein. This gene is responsible for the natural immune response and transcription factor nuclear factor kß (NFkß) activation in apoptosis. One-third of CD patients are NOD2/CARD15 gene mutation carriers [2]. Ulcerative Colitis (UC) is more common in families that have individuals with UC and in specific ethnicities, such as Jewish. This indicates that the disease has a genetic basis [3]. Although more than 30 IBD-related genes have been determined, the roles of these genes are not completely described. Pyrin and NOD2/CARD15 proteins are structurally similar and have a key role in apoptosis regulation, cytokine processing, and inflammation [4].

Familial Mediterranean Fever (FMF) is the prototype inflammatory clinical syndrome and is characterized by joint, chest, and abdominal pain. The pyrin protein, which is also known as marenostrin, is encoded by the MEFV gene. Experiments performed using animal models and cell lines as well as the presumed structure of pyrin and the presence of certain protein domains suggests that the wild type of the protein has anti-inflammatory properties [5]. Pyrin functions via its CARD domain. Mutations in the MEFV gene are responsible for diseases of innate immunity and associated with activation of the IL-1β pathway, allowing an uninterrupted inflammatory cascade and resulting in attacks of severe inflammation [6].

The prevalence of FMF in Turkey is 1/1000, and the carrier frequency is 1/5. The most frequent mutation among symptomatic FMF cases is M694V. M694V mutation ratios are 3% and 51% in healthy and symptomatic patients, respectively. Other mutations are 45% M694V; 13% M680I; 11% V726A; 7% M694I; 12% E148Q; 5% M680I; 3% M694V, and 2% V726A [7].

MEFV gene mutations causing FMF can also be found in other autoimmune diseases. It is considered that MEFV could be a potential IBD consistent with both the epidemiological and clinical data. FMF and IBD have similar clinical and biological features. Chronic inflammation episodes occur during the course of both diseases and neutrophil migration and collapsed apoptosis mechanisms are encountered in defected areas [5].

IBD and FMF are repetitive diseases with periodic symptoms. Genetic screening is needed to determine MEFV gene mutations; especially among Mediterranean populations given that FMF is more frequently observed in IBD patients in the Mediterranean region. MEFV mutations affect the disease course of IBD patients [8]. Epidemiological findings among non-Ashkenazi Jewish indicate that IBD is more common and causes more severe symptoms in patients with FMF [3]. Mutations in genes like MEFV can cause severe in-

flammatory diseases and serve a critical function in CD and UC onset. MEFV expression increased in direct proportion to the severity of inflammation in previous experiments using animal models of colitis's, such as CD and UC. MEFV's role in inflammatory diseases other than IBD has also been shown [8]. It was also reported that MEFV mutations were mostly detected in Henoch–Schonlein purpura, polyarteritis nodosa, acute rheumatic fever, and juvenile idiopathic arthritis [4].

Fidder et al. identified that M694 mutation was the most frequent in CD-FMF cases [9] while Salah et al. asserted this distinction for E148Q [10]. Karban et al. showed that there were no differences between CD cases and control groups for MEFV mutations; however, they reported that E148Q was related to perianal disease in CD cases [11]. FMF was diagnosed clinically and genetically in 6 of 46 IBD cases (23 CD, 23 UC) in our clinic. Three of these cases were UC diagnosed, and 3 of these cases were patients with CD. All 3 CD cases were M694V homozygous positive. Two of 3 UC patients were M694V homozygous positive. One UC patient was homozygous-positive with respect to D102D, G138G, and A65A in exon 2, and R314R in exon 3. The third UC patient was resistant to therapy and had abdominal pain with fever, which was controlled with colchicine treatment. Complete cure was obtained by mesalazine therapy in cases of FMF resistant to colchicine.

1.2. The Relation Between Fmf Gen Polymorphisms and Ibd

The relations between IBD and MEFV gene mutations have been evaluated in many experiments, but no clinical or laboratory data on MEFV gene polymorphisms and its relation with the high-risk groups in IBD cases were found in the literature. MEFV polymorphisms are more frequent than healthy population in other autoimmune diseases. In this study, FMF gene polymorphism was investigated in 46 cases of IBD. When we compared the frequencies of alleles between UC and CD patients, we observed a trend indicating a higher frequency of the C allele of the D102D T>C, G allele of the G138G A>G, A allele of the A165A C>A, and A allele of the R202Q G>A in UC patients. However, wild type R202Q G>A was observed in most CD patients. Moreover, an association was detected between heterozygous carriers for R314R C>T in exon 3 and those having a significantly higher risk of UC. No significant difference in genotype or allele frequencies of R314R C>T was observed in UC cases compared to that in CD. More interestingly, we observed a high degree of linkage disequlibrium between the two studied SNP's in our UC study group. Marginally significant differences were observed in the frequency of carriers of D102D T>C/R314R C>T haplotype between UC and CD. This data also suggests that haplotype increases the risk of having UC.

Basarslan et al. showed that D102D, G138G, and A165A polymorphisms are more frequents in FMF cases [12]. In another study on FMF patients with G138G polymorphism, it was reported that these patients were more susceptible to amyloidosis [13]. Oksuz et al. found A165A and G138G more frequently in FMF cases but could not find any relation with FMF clinically [14]. Similarly, Ozturk et al. found no relation between R202Q polymorphism and FMF clinically [15]. The other possibility for the manifestation of this phenotype is if a patient is carrying a combination of polymorphisms and mutation that favor more inflammation and either potentiate the inflammatory response and act as a predisposing genetic factor or have a more aggressive course through a complex genetic trait.

It is considered that R202Q is a common but not pathogenic mutation. Previous studies have not shown the clinical significance of R202Q, but in some studies it is considered to be one of the causes of disease in cases where the mutation is homozygous [16]. Ozturk et al. reported 2 amyloidosis cases that were related to homozygous R202Q [14]. E148 mutation frequency is 9–27% in Turkey [17]. Matsuda et al. determined periodic peritonitis and colchicin response relations with E148Q, R202D, P369S, and R408Q mutations in exon 2 and 3 in Systemic lupus erythematosus cases [17]. Whether E148Q is the main gene that causes the disease or just a polymorphism is still unclear. Ben-Chetrit and Tchernitchko et al. reported that E148Q is a polymorphism and has no relation with the disease [18].

Fidder et al. reported that FMF-CD patients have more frequent attacks, higher amyloidosis development, and earlier CD onset than CD patients without FMF [9]. We did not detect amyloidosis development in any IBD-FMF cases. Unlike the literature, age of diagnosis was higher in IBD-FMF patients than IBD patients. We consider that the similarity between the diseases may cause complication and end with later diagnosis.

2. Conclusion

Although it is still unclear if MEFV gene variants affect perpetuation of IBD, some MEFV allele combinations might contribute to IBD via the same inflammatory pathways as FMF. In our study, the frequency of MEFV gene variants was higher in the UC cases compared to the healthy population. It has been shown that it is necessary to broaden the scope of haplotyping studies to determine the high-risk groups of UC and provide better genetic counseling. Furthermore, if the acute-phase reactants are high despite treatment, IBD and FMF may be considered to be occurring simultaneously. Future studies with large sample sizes will elucidate the mechanisms and confirm the possible association seen herein.

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