Editorial

Can the Prevalence of Symptoms in Patients with Inflammatory Bowel Disease be Predicted by the Analysis of Multidrug Resistance Gene 1 Polymorphisms?

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Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory disorders of the gastrointestinal tract that have a significant lifelong impact on a patient's quality of life with a highly variable and uncertain clinical course.[1] The prevalence rate of these inflammatory bowel diseases (IBDs) reach up to 396/100,000 people, with a remarkable increased globalization together with other "Western disorders."[2] Although the etiology of IBD is poorly understood, it is thought to arise from dysregulation of both the innate and adaptive immune systems; leading to an abnormal inflammatory response to host's microbiota in a genetically susceptible individual. Moreover, there is accumulating evidence that genetic factors are implicated in the development of IBD, with the multidrug resistant gene (*MDR1* or ABCB1) as an interesting candidate gene for the pathogenesis of IBD. *MDR1* is located at 7q21.1 and encodes for the membrane transport protein P-glycoprotein (Pgp), which functions as an Adenosine Triphosphate-dependent efflux transporter pump. Pgp is highly expressed in the intestinal epithelium and influence the pharmacokinetics of many drugs and xenobiotics (e.g., glucocorticoids), and likely plays a role in the modulation of host-bacteria interactions.[3] First insight into the pathogenesis of IBD comes from the description of spontaneous colitis in *mdr1a* knock-out mice with a pathology similar to that of human IBD under pathogen-free conditions.[4] This finding, combined with the report that *MDR1* gene expression is significantly reduced in the colonic tissue of UC patients, make this gene an excellent positional and functional IBD candidate gene.

MDR1 is polymorphic, with more than 50 single nucleotide polymorphisms (SNPs) in the coding region of the gene.[5] The number and frequency of SNPs and haplotypes observed varies by ethnicity. Two SNPs, namely the triallelic G2677T/A (rs2032582) in exon 21 and C3435T (rs1045642) in exon 26, have been shown to correlate with Pgp expression. Association of these SNPs with both CD and UC, either as a single marker or combined, has been extensively studied. However, following initial positive associations subsequent studies have yielded contradictory results.[6,7] Moreover, C1236T, G2677T/A and C3435CT SNPs occur frequently and have strong linkage, creating a common haplotype.[5] Two recent meta-analysis of the available findings evaluating the three mentioned *MDR1* polymorphisms with susceptibility to IBD coincide in showing a slight, but significant association for the C3435T variant in UC, in contrast no association in CD patients or in IBD patients as a whole was found.[6,7]

During the past decade the incidence of IBD, especially UC, appears to be increasing in Iran, reaching a similar incidence to that of developing countries, with differences in the distribution pattern of IBD susceptibility genes in various ethnicities; however, the infrequency of CD in Iran is noted.[8] This tendency has been suggested to be associated with the gradual adoption of a Western life-style. Considering studies on *MDR1* gene polymorphisms world-wide, allele and genotype frequencies of C3435T polymorphism depends strongly on the ethnicity of the investigated population. Therefore, it is highly justified to investigate the association of *MDR1* polymorphisms with susceptibility to IBD in a country like Iran, which is a state with different ethnicities and a wide geography.

In this issue of the Saudi Journal of Gastroenterology, a study by Bonyadi *et al.*,[9] assessed the association of C3435T polymorphism of *MDR1* with the risk of developing IBD in 116 patients from the Iranian Azeri Turk ethnic group who inhabit northwestern parts of Iran. The authors were unable to get significant differences in genotype or allelic distribution between patients and control groups, even when they considered UC and CD patients separately. Their results contrast with a case-control study including 300 UC Iranian patients carried out in Tehran, which showed that the frequencies of the 3435T allele and homozygote TT genotype were significantly higher in UC patients compared to the controls,[10] as previously reported in western countries. However, the article of Bonyadi *et al.*,[9] demonstrates an association between C3435T variant and

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the risk of presenting typical intestinal signs and symptoms of IBD. According to their results, patients with TT genotype and carriers of 3435T allele are more susceptible to suffer abdominal pain and persistent diarrhea ($P < 0.02$). Similarly, the frequency of 3435T allele was higher in patients who reported vomiting and dysentery, although the value did not reach statistical significance. Furthermore, of note is the slight predominance of the 3435T allele frequency observed in healthy controls (53.8% vs. 46.1% of 3435C). Authors performed comparisons of allele frequency distribution of C3435T with those reported for different populations and ethnic groups of the world. However, they did not make a comparative analysis with C3435T population frequencies reported for other Iranian ethnic groups and populations, where C allele frequencies range from 43.7% to 66.5%.[10-13] Another weakness of the study is the relatively small sample size that reduces the power to detect a possible effect. Furthermore, the article does not go into details with regards to information about the IBD phenotype based on clinical and paraclinical parameters, including disease status (e.g., active, in remission or relapse). Nonetheless, this data adds to the growing literature needed to draw secure conclusions regarding the association of *MDR1* variants and development of IBD, further emphasizing the importance of replication of results of genetic studies in different ethnic groups. In conclusion, the study of Bonyadi *et al*., raises the possibility that the analysis of genetic polymorphisms can be used to predict the severity of the symptoms and signs of IBD; thus, this information could be used to provide a better quality of life to IBD patients.

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