

Effect of the C3435T Polymorphism of the Multidrug Resistance 1 Gene on the Severity of Inflammatory Bowel Disease in Iranian Azeri Turks

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ABSTRACT

Background/Aim: Multidrug resistance 1 (MDR1) gene encodes for P-glycoprotein (P-gp), a transmembrane efflux pump transferring both exogenous and endogenous substrate from the cells. In the human gastrointestinal tract, P-gp is found in high concentrations on the epithelial cells of the colon and small intestine. It is hypothesized that the expression level of MDR1 gene is related to susceptibility of both forms of inflammatory bowel disease (IBD). The aim of this study was to investigate the association of C3435T Single Nucleotide Polymorphism in IBD patients with/without clinical symptoms in Iranian Azeri Turks. **Settings and Design:** A total of 116 patients with IBD and 92 healthy subjects were analyzed. **Materials and Methods:** We investigated the distribution of MDR1 C3435T polymorphism via polymerase chain reaction – Restriction Fragment Length Polymorphism technique. **Statistical Analysis Used:** All statistical analyses were calculated with the SPSS for Windows 16.0. The Fisher exact test was used to test for departure from Hardy-Weinberg equilibrium of the genotype frequencies ($P > 0.05$). **Results:** The data showed that IBD patient with homozygous variant carrying MDR1 3435 T/T genotype has elevated risk for development of routine IBD clinical symptoms like Abdominal pain ($P = 0.005$) and chronic Diarrhea ($P = 0.013$) compared with MDR1 3435 C/C homozygotes who has reduced risk for development of IBD symptoms. **Conclusions:** Our data showed that patients with MDR1 3435 T/T are more susceptible to the development of some routine IBD clinical symptoms ($P < 0.05$). This study suggests a protective role for the MDR1 3435 C/C versus MDR1 3435 T/T genotype and C versus T allele for the progression of IBD in this cohort.

Key Words: Azeri Turks, C3435T polymorphism, inflammatory bowel disease, multidrug resistance gene, P-glycoprotein

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Crohn's disease (CD) and ulcerative colitis (UC) are the two main forms of inflammatory bowel diseases. UC and CD are relapsing-remitting chronic inflammatory disorders sharing overlapping clinical features.^[1] Large intestine (colon) is typically the only affected site in UC while CD is a non-infectious chronic inflammatory disorder that the inflammation can occur anywhere

along the digestive tract from the mouth to the anus. Inflammatory bowel disease (IBD) is characterized by abdominal pain, diarrhea, rectal bleeding, and weight loss.^[2] Both UC and CD have a complex etiology involving multiple genetic factors, environmental factors and immune dysregulations.^[3] Environmental factors such as cigarette smoke, dietary components, infectious microbes, sanitation, and hygiene or contact with pets remarkably increase the incidence of IBD.^[4] Involvement of genetic factors in the IBD pathogenesis has been confirmed by the observations performed on mono and dizygotic twins and familial aggregation of the disease. In Addition, a positive family history is still the largest independent risk factor for the disease.^[5-12] The results of studies on the human genome demonstrated that the human multidrug resistance 1 gene (MDR1) is the most likely locus susceptibility for IBD.^[13-15]

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MDR1 is located on the long-arm of chromosome 7 at q21.1, consists of a core promoter region, 28 exons, and encodes a 170KD P-glycoprotein (P-gp). P-gp is the Adenosine Three Phosphate binding cassette super family of transporters and resides in the plasma membrane.^[16-19] Human P-gp functions as a transmembrane efflux pump, thereby moving inflammatory factors, and drugs from the intracellular to the extracellular domain. In the human gastrointestinal tract, P-gp is found on apical surfaces of superficial columnar epithelial cells of the colon, distal small bowel, small biliary ductules, and small pancreatic ductules.^[20] Hoffmeyer *et al.*, found that C3435T have a correlation with P-gp expression in the duodenum. Individuals with the CC genotype had higher levels of P-gp expression compared to individuals with the TT genotype and heterozygote's had intermediate expression levels. The mechanism by, which the T allele results in lower duodenal P-gp expression is unknown, but it is hypothesized that C3435T may be linked to other variants in the MDR1 gene.^[21]

Different ethnic populations have different Single Nucleotide Polymorphism frequencies at the same position. The aim of this study was the association of C3435T polymorphism of MDR1 gene with the presence of clinical symptoms in IBD patients from Iranian Azeri Turks ethnic group.

MATERIALS AND METHODS

In this study, a total of 208 individuals of Iranian Azeri Turks (116 patients with IBD and 92 healthy subjects) were analyzed. Samples selection and diagnosis of disease was made according to clinical criteria of IBD.^[22]

A standard questionnaire was designed including, demographics, family history, and the presence of IBD symptoms and the data were gathered between 2009 and 2012. Peripheral blood samples were collected from the IBD patients and the genomic Deoxyribonucleic acid (DNA) was extracted. Then amplified by polymerase chain reaction (PCR) to obtain the fraction of 248-bp that included the polymorphic region C3435T, using the primers sense 5'-TGC TGG TCC TGA AGT TGA TCT GTG AAC-3' and antisense 5'-ACA TTA GGC AGT GAC TCG ATG AAG GCA-3' (South Korea). The conditions for the PCR reaction were initial denaturation at 94°C for 5 min followed by the 35 cycles of denaturation at 94°C for 1 min, annealing at 58°C for 1 mins, and extension at 72°C for 1 min, with a final extension at 72°C for 5 mins.^[23] The identification of SNP C3435T of the MDR1 gene was determined by digestion with the restriction enzyme MboI (Fermentase, Germany), using 1 unit of enzyme and 5 µL related buffer and 10 µL of the PCR product in proper drain plug and incubating the reaction mixture at 37°C overnight. The genotype was identified by electrophoresis on a 10% polyacrylamid gel and comparing it with a 100-bp marker stained with ethidium

bromide and visualized under ultraviolet light. The enzyme MboI promoted the cleavage of DNA producing specific bands observed on the gel, where CC genotype was disclosed as the fragments of DNA of 172, 60 and 16 bp, the TT demonstrated two fragments of 232 bp and 16 bp and the computed tomography (CT) displayed four fragments of 16, 60, 172, and 232 bp. The photographic documentation was performed using a digital camera.

In this study, all statistical analyses were calculated with the SPSS for Windows 16.0. The Fisher exact test was used to test for departure from Hardy-Weinberg equilibrium of the genotype frequencies ($P > 0.05$). The odds ratios (OR) and confidence intervals (CI) at the 95% significance level were calculated for all data. P values < 0.05 were regarded as significant.

RESULTS

For assessment of C3435T polymorphism of MDR1 gene in IBD patients, a total of 208 individuals were analyzed. 116 patients with IBD (21-69-years-old, 59 males [50.9%], 57 females [49.1%]) and 92 healthy volunteers (16-74-years-old, 44 males [51.7%], 41 females [48.2%]) were included in this study.

Genotype analyses of MDR1 C3435T polymorphism in this cohort showed that 22.4% of patients were homozygous MDR1 3435C/C, 25.8% were homozygous MDR1 3435T/T and 51.7% were heterozygous MDR1 3435 C/T. Allele frequency determination showed a frequency of 48.2% for the wild variant C allele and 51.7% for the polymorphic variant T allele. In healthy subjects, MDR1 3435C/C genotype was found in 19.5%. The heterozygous MDR1 3435C/T genotype was 53.2% and homozygous MDR1 3435 T/T genotype was observed in 27.1%. The frequency of C and T allele were 46.1% and 53.8% respectively.

Comparison of the allelic and genotypic frequencies between patients with IBD and control group revealed no genotypic and allelic association between cases and controls for C3435T polymorphism in this cohort (C/C; $P = 0.291$, C/T; $P = 0.383$, T/T; $P = 0.380$, C; $P = 0.355$, T; $P = 0.416$) [Table 1]. Comparison of the allelic and genotypic frequencies between UC subgroup and control group showed no significant association between cases and controls for C3435T polymorphism in this cohort [Table 2].

For assessment, the relation between genotype and clinical parameters, the allelic and genotypic frequencies of this polymorphism between controls and patients with/without symptoms were evaluated. This data showed that there was a significant difference in genotype distribution and allelic frequency among several groups [Table 3]. Patients carrying MDR1 3435T/T genotypes are more susceptible

Table 1: Genotypic and allelic frequencies of C3435T MDR1 polymorphism

Genotype and allele	IBD (n=116)		Control (n=92)		Odds ratio (95% CI)	P value
	N	%	N	%		
	CC	26	22.4	18		
CT	60	51.7	49	53.2	0.942 (0.520-1.704)	0.383
TT	30	25.8	25	27.1	0.935 (0.467-1.838)	0.380
C	112	48.27	85	46.1	1.091 (0.603-1.976)	0.355
T	120	51.72	99	53.8	0.919 (0.508-1.664)	0.416

MDR1: Multidrug resistance 1, IBD: Inflammatory bowel disease, CI: Confidence interval, CC: MDR1 3435C/C, CT: MDR1 3435C/T, TT: MDR1 3435T/T

Table 2: Allele and genotype frequencies of MDR1 C3435T polymorphism in Iranian patients with UC

Genotype and allele	UC (n=97)		Control (n=92)		Odds ratio (95% CI)	P value
	N	%	N	%		
	CC	23	23.7	18		
CT	50	51.5	49	53.2	0.934 (0.516-1.691)	0.372
TT	24	24.7	25	27.1	0.882 (0.446-1.743)	0.326
C	96	49.4	85	46.1	1.141 (0.631-2.067)	0.310
T	98	50.4	99	53.8	0.873 (0.482-1.579)	0.346

MDR1: Multidrug resistance 1, UC: Ulcerative colitis, CI: Confidence interval, CC: MDR1 3435C/C, CT: MDR1 3435C/T, TT: MDR1 3435T/T

Table 3: Genotype and allele distribution of MDR1 C3435T polymorphism between IBD patients and clinical characteristics

Features	C/C	C/T	T/T	C	T
Fever n=116					
With (%)	19	61.9	19	49.95	49.95
Without (%)	23.2	49.5	27.4	47.95	52.15
Odd ratio	0.777 (0.371-1.619)	1.657 (0.909-3.028)	0.622 (0.303-1.271)	1.083 (0.599-1.960)	0.916 (0.506-1.657)
P value	0.290	0.039	0.107	0.438	0.341
Vomiting n=116					
With (%)	6.7	73.3	20	43.35	56.65
Without (%)	24.8	48.5	26.7	49.05	50.95
Odd ratio	0.218 (0.079-0.575)	2.915 (1.549-5.510)	0.686 (0.336-1.396)	0.795 (0.438-1.441)	1.258 (0.694-2.283)
P value	0.000	0.000	0.170	0.222	0.175
Rectal bleeding n=116					
With (%)	21.6	52.9	25.5	48.05	51.95
Without (%)	23.1	50.8	26.2	48.5	51.5
Odd ratio	1.176 (0.588-2.354)	1.088 (0.601-1.969)	0.964 (0.488-1.905)	0.982 (0.543-1.777)	1.018 (0.563-1.842)
P value	0.266	0.351	0.455	0.525	0.475
Abdominal pain n=116					
With (%)	15.3	50.8	33.9	40.7	59.3
Without (%)	29.8	52.6	17.5	56.1	43.8
Odd ratio	0.426 (0.201-0.896)	0.930 (0.514-1.684)	2.418 (1.189-4.948)	0.536 (0.294-0.976)	1.866 (1.024-3.406)
P value	0.008	0.410	0.005	0.012	0.011
Dysentery n=115					
With (%)	14.6	53.7	31.7	41.4	58.5
Without (%)	25.7	51.4	23	51.4	48.7
Odd ratio	0.494 (0.228-1.065)	1.097 (0.606-1.986)	1.554 (0.792-3.056)	0.671 (0.369-1.218)	1.491 (0.821-2.712)
P value	0.023	0.383	0.094	0.084	0.076
Chronic diarrhea n=116					
With (%)	11.1	50	38.9	36.1	63.9
Without (%)	24.5	52	23.5	50.5	49.5
Odd ratio	0.385 (0.165-0.884)	0.923 (0.510-1.670)	2.073 (1.075-4.009)	0.554 (0.302-1.014)	1.806 (0.986-3.312)
P value	0.009	0.444	0.013	0.026	0.020

MDR1: Multidrug resistance 1, IBD: Inflammatory bowel disease, CC: MDR1 3435C/C, CT: MDR1 3435C/T, TT: MDR1 3435T/T

to develop severe clinical features of IBD rather than those carrying MDR1 3435C/T or MDR1 3435C/C genotypes [Table 3].

In order to find the relation between genotype and severity of disease, comparison between genotypic

frequencies of patients with/without particular symptoms of IBD was performed. The results showed significant differences between patients with/without abdominal pain (C/C; $P = 0.008$, T/T; $P = 0.005$), dysentery (C/C; $P = 0.023$) and chronic diarrhea (C/C; $P = 0.009$, T/T; $P = 0.013$) [Table 3].

DISCUSSION

In spite of vast investigations about genetic and epigenetic of IBD, the etiology of IBD still remains unknown. One of the proposed genes associated with IBD is MDR1 gene, which encodes P-gp in the gastrointestinal tract.^[24] This is the first study, which evaluate the frequency of allelic variants of 3435C > T polymorphism in Azeri Turkish patients with IBD from northwest of Iran.

In this study, no significant difference in the frequency of MDR1 genotypes between IBD patients and healthy controls were found. However, our data showed statistically significant association of TT genotype with the development of some of IBD features such as abdominal pain and chronic diarrhea among patients in this cohort.

Several studies have shown an association of MDR1 gene polymorphism with different diseases such as IBD, acute lymphoblastic leukemia, gastric cancer, colorectal cancer, and familial mediterranean fever.^[25,26] In previous studies, the frequencies of C allele of MDR1 C3435T polymorphism in different populations such as British Caucasian (48%),^[23] French (57%),^[27] German (52%),^[28] Portuguese (43%),^[25] Spanish (52%),^[29] UK (48%),^[25] Romania (51%),^[30] Chinese (56%),^[31] Indian (38%),^[32] Japanese (61%),^[33] Ghanian (83%),^[25] Kenyan (83%),^[25] Sudanese (73%),^[25] New Zealander (47%)^[34] has been reported. Results of our study on Iranian Azeri Turkish ethnic group showed that in the control group the frequency of T allele was higher than that of C allele (53.8% vs. 46.1%). In this regard, our population is similar to that of Portuguese and New Zealander populations and lowers than British Caucasian, French, German, Spanish, Romania, Chinese, Indian, Japanese, Ghanian, Kenyan, and Sudanese populations.

In this study, patient group showed a higher frequency of CC Genotype compared to control group (22.4% vs. 19.5%), but no association for CC genotype frequencies in patients and control group was found (OR = 1.192, confidence interval CI [0.571-2.491], $P = 0.291$). Our results are in accordance with the study of this polymorphism in German population, which indicated a higher frequency of the CC genotype in patients with UC than in healthy individuals (29.2% vs. 22.2%).^[9] In contrast with our results, another study of this polymorphism in Iranian population indicated higher frequency of TT Genotype in IBD patients compared to controls ($P = 0.044$, OR = 1.62).^[35]

Ho *et al.*, reported a statistically significant association between UC and a higher frequency of the TT genotype ($P = 0.04$, OR = 1.60) and T allele ($P = 0.02$, OR = 1.28) as well.^[36] Another study in German population demonstrated two fold

increase in the risk of UC development for TT homozygotes.^[37] In addition, the results of a meta-analysis study involving 7000 individuals were revealed that the UC risk was significantly associated with the 3435T allele ($P = 0.013$).^[38]

Results of our study suggest that IBD patients with C/C genotype have reduced sensitivity to some identified symptoms of IBD such as vomiting while T/T homozygotes are more susceptible to chronic diarrhea and abdominal pain. Therefore, the study suggests a protective role for the C/C and C/T genotype in development of IBD complications. On the other hand, T/T genotype probably is a risk factor for progression of IBD patients from Iranian Azeri Turks.

CONCLUSION

In conclusion, results of the present study showed significantly increased risk for IBD symptoms in 3435 T/T homozygotes versus C/C homozygotes. For future investigation of the role of MDR1 gene polymorphism in the pathogenesis of IBD, studies should be carried out with more subjects and precious clinical parameters.

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