The importance of C1236T polymorphism in the *ABCB1/MDR1* gene in assessment of susceptibility to inflammatory bowel diseases in the Polish population

Znaczenie polimorfizmu C1236T genu *ABCB1/MDR1* w ocenie podatności na nieswoiste choroby zapalne jelit w polskiej populacji

Michał Dudarewicz[1], Małgorzata Barańska[1], Mariola Rychlik-Sych[1], Radzisław Trzciński[2], Adam Dziki[2], Jadwiga Skrętkowicz[1]

[1]Department of Pharmacogenetics, Medical University of Lodz, Poland
[2]Department of General and Colorectal Surgery, Medical University of Lodz, Poland

Prz Gastroenterol 2013; 8 (1): 38–43
DOI: 10.5114/pg.2013.34181

Key words: inflammatory bowel diseases, P-glycoprotein.
Słowa kluczowe: nieswoiste choroby zapalne jelit, glikoproteina P.

Address for correspondence: Michał Dudarewicz MSc, Department of Pharmacogenetics, Medical University of Lodz, 1 Muszyńskiego St, 90-151 Lodz, Poland, phone: +48 42 677 91 77, fax: +48 42 678 83 98, e-mail: michal.dudarewicz@stud.umed.lodz.pl

Abstract

Introduction: It has been suggested that polymorphism in the *ABCB1/MDR1* gene, which encodes P-glycoprotein (P-gp), may be involved in the development of inflammatory bowel diseases (IBD). One of the *ABCB1/MDR1* gene polymorphisms that potentially influence the P-gp protection against xenobiotics is the C1236T mutation.

Aim: To evaluate whether the C1236T polymorphism is related to higher predisposition towards development of IBD, including ulcerative colitis (UC) and Crohn's disease (CD), in a Polish population.

Material and methods: This retrospective study involved a total of 155 individuals of Caucasian origin (85 patients with IBD and 70 healthy volunteers) from central Poland. The C1236T polymorphism was analyzed by using the polymerase chain reaction – restriction fragment length polymorphism (PCR-RFLP) method.

Results: Our results showed that odds ratios (ORs) for disease development (IBD, UC) were elevated in the 1236CT genotype carriers and equaled 1.26 for IBD and 1.58 for UC. In individuals with the variant 1236T allele respective ORs equaled 1.08 for IBD, 1.11 for UC, and 1.05 for CD. The observed differences in both genotype and allele frequencies were not significant.

Conclusions: In this study the C1236T polymorphism in the *ABCB1/MDR1* gene has been shown not to be a relevant factor that may predispose towards inflammatory bowel diseases in a Polish population. A lack of relationship between

Streszczenie

Wstęp: Ostatnio w kręgu zainteresowań badaczy znalazł się polimorfizm genów kodujących białka zaangażowane w detoksykację organizmu jako potencjalny czynnik wpływający na rozwój nieswoistych chorób zapalnych jelit (NChZJ). Gen *ABCB1/MDR1* odpowiada za syntezę glikoproteiny P, jednego z najważniejszych i najlepiej poznanych transporterów ksenobiotyków. Zaobserwowano, że z mutacją C1236T wiążą się międzyosobnicze różnice w odpowiedzi na leki, co wskazywałoby na zmianę w aktywności transportowej glikoproteiny P u nosicieli zmutowanego allela T.

Cel: Określenie, czy występowanie polimorfizmu C1236T jest związane z większą predyspozycją do zachorowania na NChZJ, w tym wrzodziejące zapalenie jelita grubego (WZJG) oraz chorobę Leśniowskiego-Crohna (ChLC), w polskiej populacji.

Materiał i metody: Badaniem objęto 155 osób (85 chorych na NChZJ oraz 70 zdrowych ochotników) pochodzących z Łodzi i okolic, u których polimorfizm genu *ABCB1/MDR1* w pozycji 1236 oznaczono metodą PCR-RFLP.

Wyniki: Względne ryzyko zachorowania wyrażone za pomocą ilorazu szans było zwiększone dla nosicieli genotypu 1236CT i wynosiło odpowiednio 1,26 dla osób z NChZJ oraz 1,58 dla osób z WZJG. Ryzyko zachorowania na NChZJ, w tym WZJG i ChLC, dla nosicieli zmutowanego allela 1236T wynosiło odpowiednio 1,08, 1,11, 1,05. Obserwowane różnice dotyczące częstości występowania poszczególnych genotypów i alleli mię-

the diseases and polymorphism of the gene for P-glycoprotein confirms the complexity of IBD pathogenesis.

dzy grupą osób chorych i grupą kontrolną nie były statystycznie istotne.

Wnioski: W badaniu wykazano, że mutacja C1236T nie jest istotnym czynnikiem predysponującym do zachorowania na NChZJ, w tym WZJG i ChLC. Brak związku między chorobami i polimorfizmem genu kodującego glikoproteiny P potwierdza złożoną etiopatogenezę NChZJ.

Introduction

Inflammatory bowel disease (IBD) is a term for a group of chronic conditions of the gastrointestinal tract, including ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis. In spite of many years' research the IBD pathogenesis still needs elucidation. Several factors – genetic, environmental, immunological and psychological – have been implicated in initiation and development of IBD [1-6]. Recently, scientific efforts have concentrated on polymorphisms of the protein-encoding genes that contribute not only to the immune response (*NOD2/CARD15*, *Hp*) but also to detoxification reactions (*PON1*, *PON2*, *NAT2*, *CYP2D6*) [1, 7-10]. Thus, mutations in the *ABCB1/MDR1* (ATP-binding cassette subfamily B member 1/multidrug resistance 1) gene have also been assessed as a potential factor that may affect the development of IBD. The *ABCB1/MDR1* gene encodes P-glycoprotein (P-gp), which is by far one of the most important and best-defined transporters of drugs and other xenobiotics, especially toxins contained in food products. Expression of the *ABCB1/MDR1* gene takes place in cells of the intestines, kidneys, liver, and the blood-brain barrier. The gene product regulates the flow of compounds of different origin (including endogenous) between the cells and their environment. P-glycoprotein pumps these particles out of the cells, thus offering protection from xenobiotics penetrating the human body [11]. Therefore, it seemed crucial to undertake a study to assess the polymorphism in the *ABCB1/MDR1* gene that may influence the expression level and P-gp activity in patients with inflammatory bowel diseases. Evaluation of the correlation between *ABCB1/MDR1* gene mutation and IBD development would enable researchers and physicians to expand the knowledge in terms of IBD pathogenesis.

The sequence of the *ABCB1/MDR1* gene includes over one hundred mutations indentified as single nucleotide polymorphisms (SNPs) [12]. The polymorphisms that are located in exons 12, 21, and 26, i.e. C1236T, G2677T/A, and C3435T, seem to have the most important clinical relevance. It has been observed that the mutation in exon 12 at position 1236 is associated with inter-individual differences in response to drugs, which would indicate a change in P-gp transport activity in carriers of the variant T allele. Like the C3435T polymorphism (the most extensively studied *ABCB1/MDR1* gene polymorphism), the mutation at position 1236 depends on exchange of cytosine to thymine and is a silent type mutation (the polypeptide sequence remains unaffected) [13]. The influence of the C1236T polymorphism on *ABCB1/MDR1* gene expression and P-gp activity still remains under investigation [11].

The discovery and analysis of polymorphisms in genes that encode transporters of drugs and other xenobiotics result in our better understanding of not only the causes of inter-individual differences in response to drugs but also the pathogenesis of certain diseases. In the past decade some studies were conducted, in which the frequency of 1236C and 1236T alleles was assessed in different healthy populations, in recipients of liver transplantation, patients with acute myeloid leukemia, and in patients with colorectal cancer [11, 14, 15].

Aim

The aim of our investigation was to evaluate whether there was an association between the C1236T polymorphism in the *ABCB1/MDR1* gene and development of IBD (including UC and CD) in a Polish population.

Material and methods

The study involved a total of 155 individuals (85 patients with inflammatory bowel diseases and 70 healthy volunteers) from the Lodz region in central Poland, in whom the *ABCB1/MDR1* genotype at position 1236 was analyzed. In the patient group there were 43 males (50.6%) and 42 females (49.4%) aged 18-83 years (average ± SD: 41.96 ±14.85 years). The patients were treated between the years 2006 and 2010 in the Department of General and Colorectal Surgery of the Medical University of Lodz. In the patient group there were 45 individuals diagnosed as having UC and the other 40 individuals as having CD. In the UC group there were 28 males (62.2%) and 17 females (37.8%) aged 20-83 years (average ± SD: 45.13 ±15.45 years) while in the CD group there were 15 males (37.5%) and 25 females (62.5%) aged 18-75 years (average ± SD: 38.40 ±13.47 years). The control group consisted of 70 healthy volunteers and there were 52 males (74.3%) and 18 females (25.7%) aged 19-75 years (average ± SD: 36.04 ±13.59 years).

Table I. Comparison of the genotype distribution in studied groups with the Hardy-Weinberg equilibrium

Tabela I. *Porównanie częstości występowania poszczególnych genotypów ABCB1/MDR1 w grupach badanych z częstością oczekiwaną, obliczoną na podstawie równania Hardy'ego i Weinberga*

	ABCB1/MDR1 genotype			χ^2	Value of *p*
	1236CC	1236CT	1236TT		
IBD patients (*n* = 85)					
$n_{obs.}$	35.0	35.0	15.0	1.397	0.237
$n_{exp.}$	32.4	40.1	12.4		
UC patients (*n* = 45)					
$n_{obs.}$	17.0	21.0	7.0	0.015	0.903
$n_{exp.}$	16.8	21.4	6.8		
CD patients (*n* = 40)					
$n_{obs.}$	18.0	14.0	8.0	2.567	0.109
$n_{exp.}$	15.6	18.8	5.6		
Control group (*n* = 70)					
$n_{obs.}$	32.0	25.0	13.0	3.668	0.056
$n_{exp.}$	28.3	32.4	9.3		

IBD – inflammatory bowel diseases, UC – ulcerative colitis, CD – Crohn's disease, $n_{obs.}$ – observed number of individuals, $n_{exp.}$ – expected number of individuals, p – significance level

The study design was approved by the local ethics committee on human research, and informed consent was obtained from all the patients.

The identification of C1236T polymorphism in the *ABCB1/MDR1* gene was carried out by using the polymerase chain reaction – restriction fragment length polymorphism (PCR-RFLP) method according to the procedure proposed by Cascorbi *et al.* [16]. The application of the *HaeIII* restriction endonuclease (EURx Ltd., Poland) allowed the detection of the wild-type 1236C allele and the variant 1236T allele in analyzed individuals. Subsequently, patients with IBD (including UC and CD) and healthy volunteers were classified as carriers of the genotype 1236CC (wild-type homozygotes), 1236CT (heterozygotes), and 1236TT (variant homozygotes).

Statistical analysis

Frequency of both alleles and genotypes in patients with IBD (including UC and CD) was compared with that observed in the group of healthy volunteers. The observed frequency of every genotype was also compared with the expected frequency that was calculated based on the Hardy-Weinberg equation. Statistical significance of differences in number of both alleles and genotypes was evaluated by using the χ^2 test. The values of $p < 0.05$ were considered as statistically significant. All calculations were performed by means of Statistica 9.1. (data analysis software system, StatSoft Inc.).

Results

Results of the evaluation of genotype distribution accordance with the Hardy-Weinberg equilibrium are presented in Table I. The observed number of 1236CC, 1236CT and 1236TT genotypes both in patients with IBD (including UC and CD) and in the control group did not differ significantly from the expected values.

In Table II, frequencies of particular *ABCB1/MDR1* genotypes for the C1236T polymorphism in studied groups are presented. The observed differences in the frequency of 1236CC, 1236CT and 1236TT genotypes between the IBD patients (including UC and CD) and the controls were not statistically significant.

The relative risk for development of IBD (including UC), expressed as the odds ratio (OR), was higher for the 1236CT genotype carriers and equaled 1.26 for IBD and 1.58 for UC. The risk was not statistically significant though ($p = 0.487$, $p = 0.242$, Table II).

Table III shows the frequencies of particular *ABCB1/MDR1* alleles for the C1236T polymorphism in the studied groups. The observed differences in the frequency of 1236C and 1236T alleles between the group of IBD patients (including UC and CD) and the control group were not statistically significant.

The relative risk, expressed as the odds ratio (OR), for development of IBD (including UC and CD) in the variant 1236T allele carriers equaled 1.08 for IBD, 1.11 for UC, and 1.05 for CD. The risk was not statistically significant though ($p = 0.744$, $p = 0.707$, $p = 0.874$, Table III).

Discussion

A special role in IBD pathogenesis is assigned to the intestinal barrier, where epithelial cells constitute a relevant element limiting access of xenobiotics to deeper layers of the intestine wall. In the course of IBD intestinal barrier dysfunction is observed [17]. The intestinal epithelium shows the expression of transporters mediating xenobiotic efflux into the intestinal lumen. One of these transporters is P-glycoprotein, which belongs to the protein superfamily denoted as ABC (ATP-binding cassette) [18]. According to Englund *et al.*, individuals with active UC have been shown to exhibit lower P-gp levels in the colon [19]. Yacyshyn *et al.* observed not only a decreased mRNA level for the *ABCB1/MDR1* gene, but also lower P-gp activity in the lymphocyte population deriving from the intestinal mucosa of patients with active UC [20]. The polymorphism of the *ABCB1/MDR1* gene at position 1236 is one

Table II. Frequency of particular *ABCB1/MDR1* genotypes for the C1236T polymorphism in studied groups (IBD, UC, CD patients and healthy volunteers)
Tabela II. *Częstość występowania poszczególnych genotypów ABCB1/MDR1 dla polimorfizmu C1236T w grupach badanych (osoby z NChZJ, WZJG, ChLC oraz zdrowi ochotnicy)*

ABCB1/MDR1 genotype	Control group (*n* = 70)	IBD patients (*n* = 85)			UC patients (*n* = 45)			CD patients (*n* = 40)		
	n (%)	*n* (%)	OR (95% CI)	*p*	*n* (%)	OR (95% CI)	*p*	*n* (%)	OR (95% CI)	*p*
1236CC	32 (45.7)	35 (41.2)	0.83 (0.44-1.57)	0.570	17 (37.8)	0.72 (0.34-1.55)	0.401	18 (45.0)	0.97 (0.45-2.12)	0.942
1236CT	25 (35.7)	35 (41.2)	1.26 (0.66-2.42)	0.487	21 (46.7)	1.58 (0.73-3.38)	0.242	14 (35.0)	0.97 (0.43-2.19)	0.940
1236TT	13 (18.6)	15 (17.6)	0.94 (0.41-2.14)	0.882	7 (15.5)	0.81 (0.30-2.21)	0.677	8 (20.0)	1.10 (0.41-2.93)	0.855

IBD – inflammatory bowel diseases, UC – ulcerative colitis, CD – Crohn's disease, n – number of individuals, OR – odds ratio, CI – confidence interval, p – significance level

Table III. Frequency of particular *ABCB1/MDR1* alleles for the C1236T polymorphism in studied groups (IBD, UC, CD patients and healthy volunteers)
Tabela III. *Częstość występowania poszczególnych alleli genu ABCB1/MDR1 dla polimorfizmu C1236T w grupach badanych (osoby z NChZJ, WZJG, ChLC oraz zdrowi ochotnicy)*

Allele	Control group (*n* = 70) (140 alleles)	IBD patients (*n* = 85) (170 alleles)			UC patients (*n* = 45) (90 alleles)			CD patients (*n* = 40) (80 alleles)		
	n (%)	*n* (%)	OR (95% CI)	*p*	*n* (%)	OR (95% CI)	*p*	*n* (%)	OR (95% CI)	*p*
1236C	89 (63.6)	105 (61.8)	0.93 (0.58-1.47)	0.744	55 (61.1)	0.90 (0.52-1.56)	0.707	50 (62.5)	0.96 (0.54-1.69)	0.874
1236T	51 (36.4)	65 (38.2)	1.08 (0.68-1.72)	0.744	35 (38.9)	1.11 (0.64-1.92)	0.707	30 (37.5)	1.05 (0.59-1.85)	0.874

IBD – inflammatory bowel diseases, UC – ulcerative colitis, CD – Crohn's disease, n – number of individuals, OR – odds ratio, CI – confidence interval, p – significance level

of the factors that potentially affect P-gp activity and expression. So far, the published results concerning a possible association between C1236T polymorphism and IBD have been scarce. The objective of this study was to evaluate whether the C1236T mutation is related to higher predisposition towards development of inflammatory bowel diseases, including UC and CD, in a population from the Lodz region in central Poland.

Our study demonstrated that there were no significant differences in frequency of both *ABCB1/MDR1* genotypes and alleles for the C1236T polymorphism between patients with IBD (including UC and CD) and controls (Tables II, III). The genotype distribution in the analyzed groups was consistent with the Hardy-Weinberg equilibrium (Table I).

Among healthy volunteers from the Lodz region in central Poland, who constituted the control group, the frequency of 1236CC, 1236CT, 1236TT genotypes was 45.7%, 35.7%, 18.6%, respectively (Table II). Frequencies of 1236CC, 1236CT, 1236TT genotypes were investigated in healthy individuals from various populations and the respective frequencies were 34.4%, 49.2%, 16.4% in a German population, 31.7%, 47.1%, 21.2% in a Czech population, 34.0%, 50.0%, 16.0% in a French population, 20.0%, 51.0%, 29.0% in a Turkish population, and 29.1%, 56.3%, 14.6% in a Polish population [13, 16, 21-23]. It has been observed that in our group of healthy volunteers from the Lodz region the 1236CC genotype occurred more frequently as compared to other populations, which may result from the different number of studied individuals.

In this study, the wild-type 1236C allele occurred with a frequency of 63.6% among individuals from the control group while the frequency of the variant 1236T allele was 36.4% (Table III). The obtained values are higher but comparable to published data concerning German and French populations (59.0% for the 1236C allele, 41.0% for the 1236T allele [16, 22]), and a Czech population (55.5% for the 1236C allele, 44.5% for the 1236T allele [21]). Jamroziak *et al.* observed that 1236C allele carriers accounted for 57.3%, and 1236T allele carriers for 42.7% in the Polish population [23]. Results of a study conducted in a Turkish population indicated more frequent occurrence of the 1236T allele (54.5%) than the 1236C allele (45.5%) [13].

Comparative analysis of frequencies of particular *ABCB1/MDR1* genotypes and alleles for the C1236T polymorphism between the group of patients with IBD,

including UC and CD, and the control group has not allowed us to state clearly that carriers of the variant 1236T allele (1236TT homozygotes and 1236CT heterozygotes) from the Lodz region in central Poland have a higher predisposition to develop the diseases. The obtained results regarding the particular genotype distribution indicate that individuals with the 1236CT genotype may have a higher risk of developing IBD. The estimated risk expressed as OR was 1.26 for IBD and 1.58 for UC, although it was not statistically significant (Table II). The 1236CT genotype occurred more frequently in patients with IBD (41.2%, $p = 0.487$), but especially with UC (46.7%, $p = 0.242$), as compared to individuals in the control group (35.7%, Table II).

The results concerning the distribution of particular *ABCB1/MDR1* alleles for the C1236T polymorphism have not allowed us to unequivocally link the presence of the variant 1236T allele in the Polish population to prevalence of the diseases. It has been observed that the 1236T allele occurred more frequently in patients with IBD (38.2%), including UC (38.9%) and CD (37.5%), as compared to individuals in the control group (36.4%, Table III). The estimated risk expressed as OR was 1.08 for IBD, 1.11 for UC, and 1.05 for CD, but was not statistically significant (Table III).

In the available literature, attempts have been undertaken to evaluate the influence of the C1236T polymorphism on expression level of the gene for P-glycoprotein. Illmer *et al.* noted the lowest *ABCB1/MDR1* expression level in patients with acute myeloid leukemia with two wild-type alleles, 1236CC, compared with 1236CT heterozygotes and 1236TT homozygotes [15]. However, Goto *et al.* did not observe any correlation between the change in the expression of the gene for P-gp and C1236T polymorphism in recipients of liver transplantation [14, 24]. In a study by Hemauer *et al.* it was indicated that in human placenta the 1236CT and 1236TT genotypes were related to decreased P-gp expression in comparison with the wild-type 1236CC genotype. However, the measured transport activity of P-glycoprotein was significantly higher in the presence of 1236TT than 1236CC genotype [25].

So far, few attempts have been made to elucidate whether the polymorphism in the gene for P-glycoprotein at position 1236 is associated with the development of inflammatory bowel diseases. Potocnik *et al.* analyzed a Slovenian population and found that carriers of both 1236TT and 1236CT genotypes possess an increased risk for UC development (OR = 1.734, $p = 0.01$) as compared to 1236CC homozygotes. The risk for development of refractory CD in individuals with the 1236TT and 1236CT genotypes was especially high and equaled 3.182 ($p = 0.03$) [26]. In a study carried out in a Caucasian population from Canterbury, New Zealand, it was indicated that 1236CT heterozygotes have a lower risk for UC development than the 1236CC carriers (OR = 0.63, $p = 0.03$). However, after stratification of all IBD patients as regards age, the authors noted that individuals under 17 years of age with the variant 1236T allele were at an increased risk for CD development (OR = 1.66, $p = 0.05$) [27]. Krupoves *et al.* analyzed children with CD aged 12.1 ±3.5 years from a Canadian population and observed a relationship between the C1236T polymorphism and stricture formation and penetrating disease ($p = 0.02$) [28].

Juyal *et al.* observed an association of the C1236T mutation with UC occurrence in a North Indian population. The 1236T allele occurred more frequently (62.6%) in patients than in individuals from the control group (56.9%). The 1236CC genotype carriers were shown to exhibit a lower risk for UC development (OR = 0.61, $p = 0.05$) as compared with the 1236TT genotype carriers. Moreover, the 1236C allele played a protective role against occurrence of the disease, especially in individuals under 29 years of age (OR = 0.65, $p = 0.02$) [29].

An analysis of *ABCB1/MDR1* polymorphisms was performed in a numerous group of patients with IBD in a Dutch population. The authors of the report found no relationship between the presence of the mutation at position 1236 and IBD together with its two main clinical forms (UC and CD) [30]. Osuga *et al.* analyzed UC patients in a Japanese population and concluded that the C1236T polymorphism neither affected UC susceptibility nor influenced the expression level of the gene for P-gp [31].

Conclusions

This report presents the results of an investigation on the association between the C1236T polymorphism and susceptibility to inflammatory bowel diseases. It is the first time that such a study has been performed in a Polish population. Our results indicate that the C1236T mutation is not a relevant factor that may predispose towards inflammatory bowel diseases, including UC and CD. A lack of relationship between the diseases and polymorphism of the gene for P-gp confirms the complex pathogenesis of inflammatory bowel diseases.

Acknowledgments

The study was financed from the European Social Fund and the National Budget within Action 2.6: The Integrated Operational Program for Regional Development in connection with the Project "Scholarships Supporting Innovative Research of Doctoral Students", by grant

No. 503/8-011-01/503-01, and by grant No. 502-03/8-011-01/502-64-031 from the Medical University of Lodz, Poland.

References

1. Baranska M, Trzcinski R, Dziki A, et al. The role of N-acetyltransferase 2 polymorphism in the etiopathogenesis of inflammatory bowel disease. Dig Dis Sci 2011; 56: 2073-80.
2. Chojnacki C, Walecka-Kapica E, Klupińska G, et al. Evaluation of the influence of fluoxetine on the psychosomatic status of patients with ulcerative colitis. Probl Ter Monitor 2011; 22: 3-12.
3. Cho JH. The genetics and immunopathogenesis of inflammatory bowel disease. Nat Rev Immunol 2008; 8: 458-66.
4. Dubois PC, van Heel DA. New susceptibility genes for ulcerative colitis. Nat Genet 2008; 40: 686-8.
5. Molodecky NA, Kaplan GG. Environmental risk factors for inflammatory bowel disease. Gastroenterol Hepatol 2010; 6: 339-46.
6. Maconi G, Ardizzone S, Cucino C, et al. Pre-illness changes in dietary habits and diet as a risk factor for inflammatory bowel disease: a case-control study. World J Gastroenterol 2010; 16: 4297-304.
7. Ince AT, Hatirnaz O, Ovünç O, et al. 1007fs, G908R, R702W mutations and P268S, IVS8^{+158} polymorphisms of the CARD15 gene in Turkish inflammatory bowel disease patients and their relationship with disease-related surgery. Dig Dis Sci 2008; 53: 1683-92.
8. Papp M, Lakatos PL, Hungarian IBD Study Group, Palatka K, et al. Haptoglobin polymorphisms are associated with Crohn's disease, disease behavior, and extraintestinal manifestations in Hungarian patients. Dig Dis Sci 2007; 52: 1279-84.
9. Karban A, Hartman C, Eliakim R, et al. Paraoxonase (PON)1 192R allele carriage is associated with reduced risk of inflammatory bowel disease. Dig Dis Sci 2007; 52: 2707-15.
10. Trzcinski R, Skretkowicz J, Dziki A, et al. Genetic polymorphisms of CYP2D6 oxidation in patients with inflammatory bowel disease. Dig Dis Sci 2010; 55: 1037-43.
11. Balcerczak E, Panczyk M, Piaskowski S, et al. *ABCB1/MDR1* gene polymorphisms as a prognostic factor in colorectal cancer. Int J Colorectal Dis 2010; 25: 1167-76.
12. Kerb R. Implications of genetic polymorphisms in drug transporters for pharmacotherapy. Cancer Lett 2006; 234: 4-33.
13. Gümüş-Akay G, Rüstemoğlu A, Karadağ A, et al. Genotype and allele frequencies of *MDR1* gene C1236T polymorphism in a Turkish population. Genet Mol Res 2008; 7: 1193-9.
14. Goto M, Masuda S, Saito H, et al. C3435T polymorphism in the MDR1 gene affects the enterocyte expression level of CYP3A4 rather than Pgp in recipients of living-donor liver transplantation. Pharmacogenetics 2002; 12: 451-7.
15. Illmer T, Schuler US, Thiede C, et al. MDR1 Gene polymorphisms affect therapy outcome in acute myeloid leukemia patients. Cancer Res 2002; 62: 4955-62.
16. Cascorbi I, Gerloff T, Johne A, et al. Frequency of single nucleotide polymorphisms in the P-glycoprotein drug transporter MDR1 gene in white subjects. Clin Pharmacol Ther 2001; 69: 169-74.
17. McGuckin MA, Eri R, Simms LA, et al. Intestinal barrier dysfunction in inflammatory bowel diseases. Inflamm Bowel Dis 2009; 15: 100-13.
18. Kaczmarski M, Kurzawski M, Droździk M. Drug transporters. Probl Ter Monitor 2008; 19: 49-58.
19. Englund G, Jacobson A, Rorsman F, et al. Efflux transporters in ulcerative colitis: decreased expression of BCRP (ABCG2) and Pgp (ABCB1). Inflamm Bowel Dis 2007; 13: 291-7.
20. Yacyshyn B, Maksymowych W, Bowen-Yacyshyn MB. Differences in P-glycoprotein-170 expression and activity between Crohn's disease and ulcerative colitis. Hum Immunol 1999; 60: 677-87.
21. Pechandová K, Buzková H, Slanař O, et al. Polymorphisms of the MDR1 gene in the Czech Population. Folia Biol (Praha) 2006; 52: 184-9.
22. Jeannesson E, Siest G, Bastien B, et al. Association of ABCB1 gene polymorphisms with plasma lipid and apolipoprotein concentrations in the STANISLAS cohort. Clin Chim Acta 2009; 403: 198-202.
23. Jamroziak K, Balcerczak E, Calka K, et al. Polymorphisms and haplotypes in the multidrug resistance 1 gene (MDR1/ABCB1) and risk of multiple myeloma. Leuk Res 2009; 33: 332-5.
24. Ieiri I, Takane H, Otsubo K. The MDR1 (ABCB1) gene polymorphism and its clinical implications. Clin Pharmacokinet 2004; 43: 553-76.
25. Hemauer SJ, Nanovskaya TN, Abdel-Rahman SZ, et al. Modulation of human placental P-glycoprotein expression and activity by MDR1 gene polymorphisms. Biochem Pharmacol 2010; 79: 921-5.
26. Potocnik U, Ferkolj I, Glavac D, et al. Polymorphisms in multidrug resistance 1 (MDR1) gene are associated with refractory Crohn disease and ulcerative colitis. Genes Immun 2004; 5: 530-9.
27. Huebner C, Browning BL, Petermann I, et al. Genetic analysis of MDR1 and inflammatory bowel disease reveals protective effect of heterozygous variants for ulcerative colitis. Inflamm Bowel Dis 2009; 15: 1784-93.
28. Krupoves A, Seidman EG, Mack D, et al. Associations between ABCB1/MDR1 gene polymorphisms and Crohn's disease: a gene-wide study in a pediatric population. Inflamm Bowel Dis 2009; 15: 900-8.
29. Juyal G, Midha V, Amre D, et al. Associations between common variants in the MDR1 (ABCB1) gene and ulcerative colitis among North Indians. Pharmacogenet Genomics 2009; 19: 77-85.
30. Oostenbrug LE, Dijkstra G, Nolte IM, et al. Absence of association between the multidrug resistance (MDR1) gene and inflammatory bowel disease. Scand J Gastroenterol 2006; 41: 1174-82.
31. Osuga T, Sakaeda T, Nakamura T, et al. MDR1 C3435T polymorphism is predictive of later onset of ulcerative colitis in Japanese. Biol Pharm Bull 2006; 29: 324-9.