Pharmacological Reports 67 (2015) 294–298

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original research article

Genetic polymorphism of ABCB1 gene (C3435T) in patients with inflammatory bowel diseases. Is there any gender dependency?

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ARTICLE INFO

Article history:
Received 28 November 2013
Received in revised form 28 September 2014
Accepted 30 September 2014
Available online 18 October 2014

Keywords:
Genetic polymorphism
P-glycoprotein
ABCB1 gene
Inflammatory bowel diseases

ABSTRACT

Background: In recent years, an increasing incidence of inflammatory bowel disease (IBD) has been reported, mainly as Crohn's disease (CD) and ulcerative colitis (UC). The individual susceptibility, the disease's course and response to the applied therapy is likely due to genetic factors such as ABCB1 gene mutations, exemplified by C3435T polymorphism.

The aim of the study was to evaluate the distribution of C3435T polymorphism regarding the gender in IBD patients and control subjects from Lower Silesia region and its possible association with IBD susceptibility.

Methods: The research was conducted in groups of 61 IBD patients and 101 healthy subjects from the Lower Silesia region. Polymorphism of C3435T was determined using PCR-RFLP method.

Results: Frequency distributions of C3435T genotype and of 3435T or 3435C gene alleles of IBD, CD or UC patients were compared to control group; each treated as a whole or split further by gender. The statistically significant correlation was discovered between gender and C3435T genotype both for IBD and CD patients, with 3435CT heterozygote prevailing in IBD and CD males.

Odds ratio calculations revealed statistically significant difference for the 3435CT genotype between control and: IBD group considered as a whole; IBD males; CD males; and for 3435TT variant between control and IBD males. Conclusions. The 3435CT genotype could be a risk factor for IBD and CD in men. The 3435TT genotype in males seems to be associated with the lower chance of IBD presence.

Introduction

Recent technical progress in methods of molecular genetics enables isolating, cloning and sequencing of genes derived from the human body, in particular the mapping of genes responsible for genetic disorders. In many cases, the hereditary background of particular diseases may be clearly identified. Hence, the early diagnosis of genetically determined disorders allows for the early commencement of the therapy leading to the improvement of patient's life quality [1]. The most frequently appearing type of genomic DNA sequence variability is the single nucleotide polymorphism (SNP) [2].

In recent years, an increasing incidence of inflammatory bowel disease (IBD) has been reported, particularly in North America and developed countries of Europe. It was manifested mainly as Crohn's disease (CD) and ulcerative colitis (UC). Hence, several studies have been commenced with the goal of determining the involvement of genetic factors in the pathogenesis of IBD [3–6]. One of the currently considered hypotheses states that in general, the predisposition to autoimmunological diseases depends not only on Major Histocompatibility Complex (MHC) genes [7,8], but also on other factors (genetic) such as mutations of Multi-Drug Resistance (MDR)-ABCB1 gene. In fact, the occurrence of both CD and UC is determined multigenically [9]. Actually, genetic (and also environmental) factors are essential, determining not only the susceptibility to the disease, but also affecting its

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http://dx.doi.org/10.1016/j.pharep.2014.09.014
1734-1140/

course and the response of an individual patient to the applied drug treatment [4–6,10].

The MDR1 gene, otherwise known as ABCB1 (ATP-binding cassette subfamily B member 1), is located on the 21st strip of the long arm chromosome 7 encoding P-glycoprotein (P-gp). Its mutations have been statistically associated within several different populations with an increased risk of the IBD incidence [11,12]. Many pre-clinical and clinical investigations have also shown that ABCB1/MDR1 genetic polymorphisms affect drug absorption, distribution and elimination. Clinically most significant polymorphisms are: cytosine transition into thymine at position 1236 of exon 12 C1236T, (rs1128503); substitution in exon 21 G2677A/T (rs2032582); and transversion in exon 26 C3435T (rs1128503). The incidence of these polymorphisms may influence changes in gene expression (C3435T), in P-glycoprotein structure (G2677T/A) or in its binding capacity (C1236T) [13,14].

The P-gp is one of transporting proteins present in the cell membrane of intestine enterocytes. It is involved in the cross-membrane transport, *efflux* type, carrying various substances from within the cell outside. It can actively transport drug particles into the intestinal cavity, diminishing the effectiveness of the drugs' bioavailability [9,15]. Two parameters are significant for the P-gp transportation function: the expression level of gene ABCB1 which determines the amount of protein produced and the P-gp functionality; and the effectiveness of substance/drug transferring through cell membranes [16].

The P-gp coding gene shows high polymorphism, with 50 SNP genetic variations and three insertion/deletions polymorphisms. It may indicate that P-gp plays a protective role in the prevention of cell apoptosis and may change immunological cellular response by promoting migration of antigen lymphnodules present in cells and hence initiating T lymphocyte response. It is possible that P-gp located in the digestive system is accountable for the pathotogenesis of IBD. Increased ABCB1 gene expression was discovered in CD patients who needed intestinal resection and in UC patients who needed colectomy due to ineffective drug treatment [17,18]. Furthermore, research has indicated that due to genetic variations in MDR1, the mutation C3435T type SNP is correlated to the susceptibility to renal cancer, Parkinson disease, therapy resistant epilepsy and the body reaction to applied HIV infection treatment [17].

It has been confirmed that substitution of cytosine (C) by thymine (T) in gene ABCB1 3435 in exon 26 is connected with the change of expression and activity of P-gp. It was observed that patients with *"wild"* genotype of ABCB1 343CC (homozygote CC) showed an expression of P-gp in the duodenum endothelium two times higher compared to individuals with ABCB1 343TT genotype (homozygote TT). On the other hand, the intermediate values of P-gp activity and expression were noted in patients with ABCB1 3435CT genotype (heterozygote CT) compared to both homozygote groups [18].

The majority of research has indicated that ABCB1 3435TT genotype occurs more often in patients with UC than in those with CD [15,19]. However, results are still not consistent.

The aim of the study was to evaluate the distribution of C3435T polymorphism regarding the gender in IBD patients and control subjects from Lower Silesia region and its possible association with IBD susceptibility.

Material and methods

The research was conducted in the group of 61 patients, age 35–60 years, with the IBD hospitalized in the Gastroenterology and Hepatology Department of the Medical University Hospital in Wroclaw, Poland and in the control group of 101 healthy subjects, aged 18–60 years, from the Lower Silesia region (Table 1). The IBD diagnosis was issued by a gastroenterologist based on endoscopic, radiological, and/or histopathological examinations in compliance with established clinical guidelines and criteria.

Table 1
Characteristic of investigated population: IBD, CD, UC and control group of healthy individuals.

Group	Number of persons	Gender	
	n	Female *n*	Male *n*
Inflammatory bowel diseases (IBD)	61(60)[a]	26	35
Crohn's disease (CD)	27	12	15
Ulcerative colitis (UC)	26 (25)[a]	12 (11)[a]	14
IBD non diagnosed as CD or UC	8	2	6
Control, healthy individuals	101	57	44

[a] For one person from IBD group and consequently from UC group the genetic evaluation failed, what was taken into account in some calculations.

The genomic DNA of patients and members of the control group were isolated from peripheral blood leukocytes using QIAamp DNA Blood Mini Kit (QIAGEN GmbH, Germany).

The polymorphism of C3435T in exon 26 of ABCB1 gene was determined in the Department of Clinical Pharmacology of Wroclaw Medical University by the modified method of Siegmund and collaborators using PCR-RFLP (Polymerase Chain Reaction – Restriction Fragment Length Polymorphism) [20]. The research was approved by The University Ethic Committee Wroclaw Medical University.

In order to evaluate frequency distribution differences between IBD, CD, UC patients and controls, and also within subgroups of IBD patients, the statistic Pearson chi-square test and the highest reliability test were conducted regarding the uniformity of genotype and allele distributions in two groups defined by gender or by specific illness. The result was statistically significant at $p < 0.05$. To acquire the probability for the disease occurrence, odds ratios (OR) for examined groups were calculated.

In order to determine whether the observed frequency distribution for alleles remains in the genetic equilibrium, the chi-square reliability test was conducted for investigated polymorphisms. In all considered patient groups, the chi-square statistics values exceeded the critical value (0.0039), hence the hypothesis on conformity to the Hardy–Weinberg distribution was rejected.

Results

For the C3435T genotype (genotypes CC, TT, CT), no statistically significant differences of frequency distributions (Pearson chi-square) were found between: female and male in the control group; IBD patients and the control group; CD and UC patients and the control group; and UC female and male group. Similarly, no statistically significant differences were found between these groups for the frequency distribution of 3435T or 3435C gene alleles.

On the contrary, the statistically significant relation was discovered in the frequency distribution for IBD patients between gender and C3435T genotype. The 3435CT heterozygote prevails in males (77.14%), whereas in females, the 3435CT and the 3435TT genotypes oscillate at similar frequency levels (respectively 40% and 44%, $p < 0.05$) (Table 2). The same tendency was observed for the CD patients group. The 3435CT heterozygote's prevails in males (86.67%), while in females, 3435CT and 3435TT genotypes oscillate at similar levels (33.33% and 41.67% respectively, $p < 0.05$).

The analysis of the allele distribution showed that 3435T allele count in patients with IBD was higher for females (64%) than males

Table 2
The frequency of ABCB1/MDR1 genotypes and alleles in healthy individuals and in analyzed groups of patients (IBD total, CD, and UC total and subgroups).

Group	3435CC genotype *n* (%) of total	3435 TT genotype *n* (%) of total	3435 CT genotype *n* (%) of total	3435C allele *n* (%) of total	3435T allele *n* (%) of total
Control total *n* = 101	**19** (18.81%)	**37** (36.63%)	**45** (44.55%)	**83** (41.01%)	**119** (58.91%)
Control female *n* = 57	**9** (15.79%)	**20** (35.09%)	**28** (49.12%)	**46** (40.35%)	**68** (59.65%)
Control male *n* = 44	**10** (22.73%)	**17** (38.64%)	**17** (38.64%)	**37** (42.05%)	**51** (57.95%)
IBD total *n* = 61(60)[a]	**8** (13.33%)	**15** (25%)	**37** (61.67%)	**53** (44.17%)	**67** (55.83%)
IBD female *n* = 26(25)[a]	**4** (16%)	**11** (**44%**)	**10** (**40%**)	**18** (36%)	**32** (64%)
IBD male *n* = 35	**4** (11.43%)	**4** (11.43%)	**27** (**77.14%**)[a,b]	**35** (50.00%)	**35** (50.00%)
CD total *n* = 27	**3** (11.11%)	**7** (24%)	**17** (62.96%)	**23** (42.59%)	**31** (57.41%)
CD female *n* = 12	**3** (25%)	**5** (**41.67%**)	**4** (**33.33%**)	**10** (41.67)	**14** (58.33%)
CD male *n* = 15	**0** (0%)	**2** (13.33%)	**13** (**86.67%**)[a,b]	**13** (43.33%)	**17** (56.67%)
UC total *n* = 26 (25)[a]	**4** (16%)	**6** (23.08%)	**15** (60%)	**23** (46%)	**27** (54%)
UC female *n* = 12 (11)[a]	**1** (9.09%)	**4** (36.36%)	**6** (54.54%)	**8** (36.36%)	**14** (63.64%)
UC male *n* = 14	**3** (21.43)	**2** (14.28%)	**9** (64.29%)	**15** (53.57%)	**13** (46.43%)

[a] For one person from IBD group and consequently from UC group the genetic evaluation failed, what was taken into account in some calculations.
[b] Results are significant at $p < 0.05$.

(50%) while 3435C allele prevails in men (50% *versus* 36%). However, the difference was not statistically significant (Table 2).

The collected data showed that the genotype and allele distribution for ABCB1 C3435T gene was not specific for UC. No statistically significant differences were found for the frequency of genotype and allele.

Odds ratio (OR) calculations for the occurrence of CC, TT and CT genotypes of ABCB1 in various study subgroups (IBD, CD and UC) compared to the control group showed statistically significant difference for: a) the 3435CT genotype which correlates better to: IBD patients considered as a whole (OR = 2.00, CI 1.04–3.84, $p < 0.04$); IBD male group (OR = 5.36, CI 1.98–14.50, $p = 0.0009$); which means a greater probability for IBD manifestation for 3435CT carriers, b) the 3435CT genotype which is more common in CD male patients (OR = 10.32, CI 2.06–51.52, $p = 0.004$) meaning greater susceptibility to CD; c) the 3435TT variant correlating less to IBD male individuals (OR = 0.20, CI 0.06–0.68, $p = 0.0099$). Hence, 3435TT means a smaller probability for IBD occurrence in men (Table 3). No statistically significant differences of OR values were found for C or T allele in IBD, CD and UC subgroups compared to the control group.

Discussion

The increasing number of the worldwide research concentrated on the influence of the gene ABCB1/MDR1 polymorphism on IBD pathogenesis showed with high certainty that there existed the genetically determined susceptibility (predisposing genotype) for IBD development in predisposed individuals.

Schaeffeler et al. proved that in healthy persons of West African and African origin living in the USA, the 3435CC genotype incidence is respectively 85% and 61%. Furthermore, they observed that within the white population living in this region the occurrence of 3435CC genotype was as rare as 26% [21]. In the investigated population from Lower Silesia, we also observed lower percentage of 3435CC genotypes (18.81%) within the control group.

Next Ardizzone et al. studies performed in the group of 560 IBD Italian patients showed correlation between the presence of 3435T allele and the occurrence of CD with lesions located in ileum and colon (OR = 3.34, over three times more than individuals with 3435C allele) [22]. On the contrary, we did not found in our study any significant correlation between the presence of a specific allele and the disease occurrence.

Table 3
Odds ratio (OR) for occurrence of IBD, CD and UC (for female and male) in comparison to control group depending on presence of CC, TT and CT genotypes of ABCB1/MDR1 gene.

Compared groups	Genotype								
	CC			TT			CT		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
IBD total/control total	0.66	0.27–1.62	0.37	0.58	0.28–1.17	0.1	**2.00**	**1.04–3.84**	**0.04**[a]
IBD/control female	1.01	0.28–3.67	0.98	1.45	0.56–3.79	0.44	0.69	0.27–1.79	0.45
IBD/control male	0.42	0.12–1.54	0.01	**0.20**	**0.06–0.68**	**0.0099**[a]	**5.36**	**1.98–14.50**	**0.0009**[a]
CD/control total	0.54	0.15–1.98	0.35	0.60	0.23–1.56	0.3	2.11	0.88–5.07	0.009
CD/control female	1.77	0.40–7.87	0.44	1.32	0.37–4.70	0.66	0.52	0.14–1.91	0.32
CD/control male	0.11	0.01–1.92	0.13	0.24	0.04–1.22	0.08	**10.32**	**2.06–51.52**	**0.004**[a]
UC/control total	0.82	0.25–2.67	0.74	0.54	0.20–1.49	0.24	1.87	0.76–4.55	0.17
UC/control female	0.53	0.06–4.69	0.57	1.06	0.28–4.05	0.93	1.24	0.34–4.53	0.74
UC/control male	0.84	0.32–2.17	0.73	0.26	0.05–1.33	0.11	2.38	0.72–7.89	0.15

[a] Results are significant at $p < 0.05$.

The study conducted by Urcelay et al. in a Spanish population showed that the presence of 3435C allele and 3435CC genotype increased the predisposition to the CD manifestation (contrary to results presented by Ardizzone et al.). In our study the susceptibility of 3435CT carriers to CD was observed, especially in male group. Moreover, authors concluded that UC individuals showed higher rate of 3435T alleles and 3435TT genotypes compared with the control group which was not observed in our study [7].

The results of the meta-analysis study performed by Onnie et al. with 7000 cases indicated a connection between the presence of mutated allele 3435T carriers and the higher UC incidence in British population (OR = 1.12, $p < 0.013$). [23]. No such correlation was reported for patients with CD.

Likewise Schwab et al. observed within a German population the higher 3435T allele and 3435TT genotype frequency in UC patients (3435TT genotype doubled the risk of UC incidence) and no such correlation for CD individuals [24].

Results referring to the UC genetic predisposition in a Greek population were reported by Gazouli et al. [25].

The specific distribution of ABCB1 genotypes, documented in the above mentioned studies suggested that their polymorphism (depending on the population) could be a differentiating susceptibility marker for IBD (CD or UC) occurrence. That is why subsequent studies were and currently are conducted related to this issue.

Outside Europe, studies performed in Japan by Osuga et al. also demonstrated much higher frequency of 3435T allele in UC patients compared to healthy individuals. Moreover, it was documented that in the older patients group, with late disease onset, the C3435T gene polymorphism was an important factor for morbidity, as opposed to the group of young patients where such a coincidence was not noted [26].

Next, the results achieved by Farnood et al. in the study performed in an Iranian population also confirmed the association (in Arabian people) between UC and the occurrence of 3435TT genotype ($p = 0.044$, OR = 1.62) and 3435T allele ($p < 0.001$, OR = 1.52). Furthermore, the correlation between the 3435CT heterozygote presence and the predisposition to clinical manifestation of UC was proved [27]. Moreover Farnood et al. postulated that the 3435CC genotype appeared more frequently in healthy populations, which suggested that it might act as the risk reducing factor for UC development. Our results did support both of these hypothesis.

The results of above presented worldwide studies, associating C3435T polymorphism with the clinical manifestation of IBD (CD or UC) were not conclusive. Many publications reported radically different observations. Contrary to Ardizzone et al., Palmieri et al. did not prove the dependence between the 3435T allele carriers and the higher UC or CD occurrence within an Italian population. Moreover, they were proponents of the hypothesis that C3435TT genotype in IBD patients did not play a significant role in response to the applied therapy [22,28]. Also Brant et al., while analyzing morbidity specific factors for an American population including patients of the Jewish origin, did not observe the population-related predisposition to UC and CD disease associated with the presence of C3435T gene polymorphism (similarly to Palmieri et al.) [13].

To the contrary, the studies in a Slavic population performed by Potočnik et al. in Slovenia showed higher occurrence of the 3435T allele of MDR1 gene in patients with UC and treatment resistant CD persons [11].

The Polish study conducted in 2002 by Jamroziak et al. investigated the distribution of C3435T genotype within a healthy Slavic population of Central Poland and reported the occurrence of: 3435CC genotype as 42%; 3435CT as 41%; and 3435TT as 17%; and the allele C3435T incidence similar to that in a Japanese population and much higher than in a Caucasian population of Western Europe [29]. Our results were different for the frequency distribution of C3435T genotype in the healthy person group. We observed: 18.9% of 3435CC genotype; 36.6% of 3435TT; and 44.6% of 3435CT carriers.

Studies performed by Kurzawski et al. in 2006 demonstrated that for inhabitants of Poland, 3435C allele was more widely distributed than 3435T allele and the frequencies of 3435CC, 3435CT, 3435TT genotypes were respectively: 22%, 51% and 27% [30]. Our results received for the control group varied from those presented in that research.

Finally, the study conducted by Dudarewicz et al. in a Polish population (with 108 IBD patients, 61 with UC and 47 with CD, and 137 healthy individuals), did not confirm (similarly as our data) any significant difference between the study and the control groups in the frequency of occurrence for any particular genotype or allele of C3435T gene [31]. However, authors observed that the percentage of 3435CC "*wild*" genotype in the control group was lower than in the IBD study group. On the contrary, in our study the percentage of 3435CC genotype was higher in the control group than in IBD, respectively 18.81% and 13.33% (the indicated difference was not statistically significant). Moreover, Dudarewicz et al. showed that 3435CC genotype occurred more often in the IBD and UC male patient groups than in the male control group (the differences were not statistically significant though). Similar results were obtained in that study for the female group with IBD and UC in comparison to the control. Our study did not confirm such observations. Authors also documented that 3435TT genotype was more often visible in the male control group than in the IBD, UC, and CD patient groups. Our data were different: in the IBD male group the 3435TT genotype incidence was lower than in control group and additionally the chance for the disease appearance (expressed as OR) was also lower. Finally authors stated that the C3435T polymorphism was not the risk factor for IBD morbidity within a Central Poland population [31].

The our data obtained from the population of the Lower Silesia region of Poland did not confirm (similarly as in the study by Dudarewicz et al.) any significant difference between the study and the control groups in the frequency for any particular genotype or allele of C3435T gene [31]. Nevertheless in our study the statistically significant correlation was demonstrated to exist for patients with IBD and CD between the distribution of the C3435T polymorphism and the patient's gender. Males who were 3435CT homozygote carriers were more susceptible for IBD and CD. Such correlation between genotype and gender was not seen in the control group. Similar result had been reported by Farnood et al. in an Arabian population [26]. Moreover, our study showed higher incidence of 3435CT genotype of ABCB1 gene in IBD males (77.14%) than in the female group (40%) ($p < 0.05$). Frequency distributions of 3435CT and 3435TT genotypes in female patients with IBD were comparable (3435CT: 40% and 3435TT: 44%) with no statistically significant difference between them. Additionally, we observed a higher chance (OR) of IBD manifestation for 3435CT carriers (OR = 2.0) and especially for males (OR = 5.36), and a lower chance for the disease occurrence in males associated with 3435TT genotype (OR = 0.20). Similar results have been obtained by Dudarewicz et al. for IBD patients as a whole and for UC persons but differences were not statistically significant. Characteristically in each our study subgroup: patients with IBD (CD and UC) and the control one, the frequency of CT genotype and allele T was higher compared to CC and TT genotypes and allele C [31]. Similar results were disclosed by Kurzawski et al. in the study evaluating the distribution of C3435T genotype in the West Pomeranian region of Poland. However, that study did not demonstrate the possible

impact of C3435T polymorphism on the predisposition to the development of IBD (UC, CD, IBD) [30].

Conclusions

The above results imply that C3435T polymorphism of ABCB1 gene plays an important role in the pathogenesis of IBD. The presence of the 3435CT genotype could be the risk factor for IBD or CD in men. On the other hand, the 3435TT genotype in males seems to be connected with lower chance of IBD manifestation.

Data obtained from the population research all over the world have raised the question if, and to what extent genetic factors including C3435T gene polymorphism affect the development of IBD. Results of studies performed in Poland and within other populations are ambiguous. Data presented here show the complexity of genetic polymorphism influence on predisposition to IBD in different population.

Based on our data and literature reports, it seems to be crucial both to evaluate and confirm the correlation between the gender susceptibility to IBD and the polymorphism of C3435T gene in relation to race and ethnicity.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

This research was financially supported by the statutory grant from Wroclaw Medical University, grant number ST-520.

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