Research Article

Genetic Polymorphisms of Multidrug Resistance Gene-1 (MDR1/ABCB1) and Glutathione S-Transferase Gene and the Risk of Inflammatory Bowel Disease among Moroccan Patients

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Inflammatory bowel diseases (IBD) are multifactorial disorders resulting from environmental and genetic factors. Polymorphisms in MDR1 and GSTs genes might explain individual differences in susceptibility to IBD. We carried out a case-control study to examine the association of MDR1 (C1236T and C3435T), GSTT1, and GSTM1 polymorphisms with the risk of IBD. Subjects were genotyped using PCR-RFLP for MDR1 gene and multiplex PCR for GSTT1 and GSTM1. Meta-analysis was performed to test the association of variant allele carriage with IBD risk. We report that GSTT1 null genotype is significantly associated with the risk of CD (OR: 2.5, CI: 1.2–5, \( P = 0.013 \)) and UC (OR: 3.5, CI: 1.5–8.5, \( P = 0.004 \)) and can influence Crohn’s disease behavior. The interaction between GSTT1 and GSTM1 genes showed that the combined null genotypes were associated with the risk of UC (OR: 3.1, CI: 1.1–9, \( P = 0.049 \)). Furthermore, when compared to combined 1236CC/CT genotypes, the 1236TT genotype of MDR1 gene was associated with the risk of UC (OR: 3.7, CI: 1.3–10.7, \( P = 0.03 \)). Meta-analysis demonstrated significantly higher frequencies of 3435T carriage in IBD patients. Our results show that GSTT1 null and MDR1 polymorphisms could play a role in susceptibility to IBD.

1. Introduction

Inflammatory bowel disease (IBD) is a multifactorial disorder of the gastrointestinal tract including Crohn’s disease (CD) and ulcerative colitis (UC). Although considerable progress has been made in the field of IBD research, the underlying etiopathogenesis is still under investigation [1]. It is assumed that inappropriate immune response to commensal intestinal bacteria associated with defective mucosal barrier related to genetic and environmental factors might play a fundamental role in the onset of IBD [2, 3]. The involvement of oxidant/antioxidant imbalance in the development and severity of IBD is well documented. Previous studies have demonstrated the role of candidate genes such as the multidrug resistance 1 (MDR1) and glutathione S-transferases (GSTs) in protecting cells against toxins, xenobiotics, or their metabolites [4]. The MDR1 gene encodes a member of the ABC transporter subfamily B, a transmembrane P-glycoprotein (P-gp) of 170 kDa, which functions as an adenosine triphosphate-dependent efflux transporter pump [5]. P-gp is highly expressed on the apical surfaces of superficial columnar epithelial cells of the colon and distal small bowel. High levels are also found in small biliary ductules and small pancreatic ductules [6]. The high constitutive levels of P-gp expression in the gut suggest a role as a protective barrier against the absorption of endogenous or exogenous toxins and possibly a putative role in modulation of host-bacterial interactions [7, 8]. Among the polymorphisms identified in MDR1 gene, the most widely investigated in IBD association studies as well as in other diseases are...
the 1236C>T (exon 12; rs1128503, Gly412Gly), 2677G>T/A (exon 21; rs2032582, Ala893Ser/Thr), and 3435C>T (exon 26; rs1045642, Ile1145Ile) with conflicting results in different populations around the world [9–11].

GSTs are phase II xenobiotic metabolizing enzymes. They play a critical role in cellular protection against reactive electrophiles and fatty acid hydroperoxides generated by oxidative stress through the conjugation with reduced glutathione. Therefore, GSTs facilitate the detoxification of cells by limiting tissue damage from free radical attack [12, 13]. GSTM1 (GST-mu 1) and GSTT1 (GST-theta 1) located on chromosomes 1p13.3 and 22q11.2, respectively, are two members of the GSTs family being most frequently studied [14, 15]. Common deletion variants (termed null) of the structural GST candidates 1p13.3 and 22q11.2, respectively, are two members of the GST family being most frequently studied [14, 15]. Common deletion variants (termed null) of the structural GSTM1 and GSTT1 genes are associated with either decreased or impaired enzyme function [16]. Several studies have demonstrated the association of GSTM1 and GSTT1 genes with the risk of various cancers including bladder, gastric, and oral cancers and chronic myeloid leukemia [17–20]. However, few studies have addressed the relationship between GSTM1 and GSTT1 polymorphisms and the susceptibility of inflammatory and autoimmune diseases such as IBD [21–23]. To the best of our knowledge, the relationship between polymorphisms in MDR1 and GSTs genes and the risk of IB has not been examined so far in the Moroccan population. Therefore, our study investigated the role of GSTM1, GSTT1, MDR1 C1236T, and C3435T SNPs in determining disease susceptibility in Moroccan patients.

2. Materials and Methods

2.1. Study Population. A total of 110 patients diagnosed with IBD at the Department of Gastroenterology, CHU Ibn Rochd (Casablanca, Morocco), were selected. Blood samples from 100 blood donors were used as controls. The diagnosis of CD or UC was established according to conventional clinical, endoscopic, radiological, and histological criteria as previously described [24, 25]. Patient's clinical and demographic characteristics were collected in a case report form (Supplementary Files) (see Supplementary Material available online at http://dx.doi.org/10.1155/2015/248060). The local ethics committee approved the study and a written informed consent was obtained from all participants.

2.2. Genotyping of MDR1, GSTM1, and GSTT1 Polymorphisms. Genomic DNA was extracted from whole blood using the salting-out method. DNA concentration and quality were analyzed using a NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, USA). Genotyping of C1236T and C3435T SNPs was done by polymerase chain reaction, restrictive fragment length polymorphism. The primer sequences, enzymatic restriction conditions, and digestion product sizes were previously described [26, 27]. To identify the genotypes of GSTM1 and GSTT1, a multiplex polymerase chain reaction (PCR) was performed, in which BCL2 gene was used as an internal control. PCR amplification condition and products sizes were previously described [28].

2.3. Meta-Analysis

2.3.1. Inclusion and Exclusion Criteria. Genetic association studies were included in our meta-analysis if they met the following criteria: (a) a case-control study design, (b) studies that evaluated the association between the MDR1 C3435T, C1236T, GSTM1, and GSTT1 polymorphisms and IBD, and (c) the study reporting sufficient data to calculate allele frequencies and odds ratios of cases and controls for carriage of MDR1 C3435T and 1236T alleles. Major exclusion criteria were (a) case-only study and review articles and (b) studies without raw data of the MDR1 and GST genotypes.

2.3.2. Pooled Studies for Case-Control Meta-Analysis. Twenty-seven case-control studies investigating MDR1 polymorphisms in IBD patients were identified through the literature search. Eighteen studies that met the inclusion criteria were retrieved in MDR1 C3435T meta-analysis (Table 1). Five of them were included in MDR1 C1236T meta-analysis (Table 2). GSTM1 and GSTT1 meta-analysis reported data from 3 of the included studies with 789 cases and 792 controls (Table 3). The risk of IB associated with the reported polymorphisms was estimated for each study by odds ratio (OR) and 95% confidence interval (95% CI). The meta-ORs were estimated using a fixed-effects model. Genetic heterogeneity was tested by Cochran’s (Q) test and I² statistics was used to quantify the between-study heterogeneity effect. When a significant Q test (Q > 0.10; I² > 50%) indicated heterogeneity across studies, data were recombined using a random-effects model to estimate common ORs. The meta-analyses were conducted by MedCalc v.11.6.1.0 software.

2.4. Statistical Analysis. Data analysis has been carried out using the statistical package SPSS version 16 (SPSS Inc., Chicago, IL, USA). Differences in distribution of demographic and clinical features of patients with respect to their genotypes were done by chi-square test or Fisher Exact Test. The same tests were used to compare the distribution of genotypes between patients and controls as well as assess the Hardy-Weinberg Equilibrium in MDR1 gene. Odds ratio (OR) with a confidence interval (CI) of 95% was calculated to measure the strength of association between C1236T, MDR1 C3435T, GSTT1, and GSTM1 and the risk of inflammatory bowel disease. A P value less than 0.05 was considered as statistically significant.

3. Results

The present case-control study reports the frequencies of MDR1 C1236T, MDR1 C3435T, GSTT1, and GSTM1 in 77 CD patients, 33 UC patients, and 100 unrelated healthy controls. The two SNPs of MDR1 did not deviate from Hardy-Weinberg Equilibrium in control subjects. Allele and genotype frequencies of C1236T and C3435T polymorphisms in patients and controls are summarized in Table 4. The distribution of genotype frequencies showed no influence on the risk of CD and UC (P > 0.05). This finding remained valid for the allele frequencies (P > 0.05). In Table 5, the consideration of the recessive model showed that carriers of 1236TT genotypes
Table 1: Pooled analysis of studies exploring the role of MDR1 C3435T in IBD.

| Study                        | Cases (event/total) | Controls (events/total) | Odds ratio | 95% CI       |
|------------------------------|---------------------|-------------------------|------------|--------------|
| Senhaji et al. 2015 (the current paper) | 75/220              | 53/120                  | 0.65       | 0.41 to 1.03 |
| Yang et al. 2015 [36]        | 121/298             | 152/446                 | 1.32       | 0.97 to 1.79 |
| Bonyadi et al. 2013 [37]     | 120/232             | 99/184                  | 0.92       | 0.62 to 1.35 |
| Brinar et al. 2013 [32]      | 304/612             | 106/238                 | 1.22       | 0.91 to 1.66 |
| Dudarewicz et al. 2012 [38]  | 77/108              | 111/137                 | 0.58       | 0.32 to 1.05 |
| Huebner et al. 2009 [30]     | 600/759             | 156/195                 | 0.94       | 0.63 to 1.39 |
| Ardizzone et al. 2007 [39]   | 180/288             | 123/210                 | 1.17       | 0.81 to 1.69 |
| Fischer et al. 2007 [29]     | 308/414             | 106/146                 | 1.09       | 0.71 to 1.67 |
| Karlsen et al. 2007 [40]     | 231/268             | 310/368                 | 1.16       | 0.74 to 1.82 |
| Fiedler et al. 2007 [41]     | 304/388             | 782/1015                | 1.07       | 0.81 to 1.43 |
| Onnie et al. 2006 [9]        | 1071/1408           | 219/280                 | 0.88       | 0.65 to 1.20 |
| Oostenbrug et al. 2006 [42]  | 757/1420            | 293/530                 | 0.92       | 0.75 to 1.12 |
| Ho et al. 2006 [43]          | 352/428             | 205/260                 | 1.24       | 0.84 to 1.83 |
| Urcelay et al. 2006 [44]     | 405/614             | 227/324                 | 0.82       | 0.61 to 1.10 |
| Palmieri et al. 2005 [45]    | 697/946             | 335/450                 | 0.96       | 0.74 to 1.24 |
| Ho et al. 2005 [46]          | 486/603             | 288/370                 | 1.18       | 0.86 to 1.62 |
| Glas et al. 2004 [47]        | 213/258             | 195/265                 | 1.69       | 1.11 to 2.59 |
| Schwab et al. 2003 [10]      | 216/275             | 201/275                 | 1.34       | 0.91 to 1.99 |
| Total (fixed effects)        | 6517/9539           | 3961/5813               | 1.03       | 0.96 to 1.12 |
| Total (random effects)       | 6517/9539           | 3961/5813               | 1.04       | 0.94 to 1.15 |

Test for heterogeneity: $Q = 26.12$; DF = 17; $I^2 = 35\%$; $P = 0.07$.

Table 2: Pooled analysis of studies exploring the role of MDR1 C1236T in IBD.

| Study                        | Cases (event/total) | Controls (events/total) | Odds ratio | 95% CI       |
|------------------------------|---------------------|-------------------------|------------|--------------|
| Senhaji et al. 2015 (the current paper) | 75/220              | 65/200                  | 1.07       | 0.71 to 1.61 |
| Yang et al. 2015 [36]        | 181/300             | 275/446                 | 0.94       | 0.70 to 1.27 |
| Huebner et al. 2009 [30]     | 686/1554            | 181/398                 | 0.94       | 0.75 to 1.18 |
| Oostenbrug et al. 2006 [42]  | 610/1420            | 228/530                 | 0.99       | 0.81 to 1.22 |
| Ho et al. 2006 [43]          | 400/856             | 236/522                 | 1.06       | 0.85 to 1.32 |
| Total (fixed effects)        | 1952/4350           | 985/2096                | 0.99       | 0.89 to 1.11 |
| Total (random effects)       | 1952/4350           | 985/2096                | 0.99       | 0.89 to 1.11 |

Test for heterogeneity: $Q = 0.78$; DF = 4; $I^2 = 0\%$; $P = 0.94$.

were more exposed to developing UC when compared to the combined 1236CC/CT genotype (OR: 3.7; CI: 1.3–10.7, $P = 0.03$). However, the dominant model showed no particular effect whatever the type of considered SNP is. As presented in Table 6, we found that GSTMI null genotype frequency was higher in CD patients without being statistically significant (OR 1.2; CI: 0.6–2.1, $P > 0.05$). The same trend was observed in UC patients (OR: 1.5; CI: 0.7–3.3, $P > 0.05$). Surprisingly, we noticed that the GSTTI null genotype was significantly associated with the risk of CD (OR: 2.5; CI: 1.2–5, $P = 0.013$) and the risk of UC (OR: 3.5; CI: 1.5–8.5, $P = 0.004$). Furthermore, the interaction between GSTMI and GSTTI showed that the combined null genotype (GSTMI null, GSTTI null) was associated with the risk of UC at the limit of the statistical level (OR 3.1; CI: 1.1–9, $P = 0.049$) (Table 7). The distribution of demographic and clinical features of CD and UC patients with respect to genotypes of GSTMI, C1236T (exon 12), and C3435T (exon 26) in MDR1 gene showed no particular trend of association (data not shown). On the other hand, frequency of the stricturing form was statistically higher in CD patients carrying the GSTTI null genotype compared to the penetrating or inflammatory forms (52% versus 33.3%; 13.6%, $P = 0.02$). However, the association between smoking status (current, former, or never smoking) and CD/UC was not influenced by genetic polymorphisms in genes encoding the GSTs metabolizing enzymes (Table 8).

Based on the studies published on MDR1 C3435T combined to our results, we observed a significant association between the T allele and IBD risk (Table 1, Figure 1). Meta-analysis of our dataset with the published studies on C1236T.
## Table 3: Pooled analysis of studies exploring the role of GSTM1 and GSTT1 in IBD.

| Study                          | Cases (event/total) | Controls (events/total) | Odds ratio | 95% CI    |
|-------------------------------|---------------------|-------------------------|------------|-----------|
| **Studies on GSTM1**          |                     |                         |            |           |
| Senhaji et al. 2015 (the current paper) | 62/110             | 51/100                  | 1.24       | 0.72 to 2.13 |
| Karban et al. 2011 [21]       | 277/574             | 300/528                 | 0.70       | 0.55 to 0.89 |
| Mittal et al. 2007 [23]       | 61/105              | 49/164                  | 3.25       | 1.95 to 5.42 |
| Total (fixed effects)         | 400/789             | 400/792                 | 0.97       | 0.80 to 1.18 |
| Total (random effects)        | 400/789             | 400/792                 | 1.39       | 0.55 to 3.53 |
| **Studies on GSTT1**          |                     |                         |            |           |
| Senhaji et al. 2015 (the current paper) | 40/110             | 17/100                  | 2.79       | 1.45 to 5.34 |
| Karban et al. 2011 [21]       | 172/574             | 97/528                  | 1.90       | 1.43 to 2.52 |
| Mittal et al. 2007 [23]       | 95/105              | 26/164                  | 5.04       | 23.23 to 109.4 |
| Total (fixed effects)         | 307/789             | 140/792                 | 3.13       | 2.49 to 3.95 |
| Total (random effects)        | 307/789             | 140/792                 | 6.26       | 1.06 to 36.87 |

## Table 4: Distribution of genotypes and alleles of MDRI polymorphisms in IBD patients and controls.

| Genotypes/alleles | Control N (%) | CD N (%) | OR (95% CI) | P value | UC N (%) | OR (95% CI) | P value |
|-------------------|---------------|----------|-------------|---------|----------|-------------|---------|
| 1236CC            | 43 (43)       | 33 (43)  | Ref.        |         | 12 (36)  | Ref.        |         |
| 1236CT            | 49 (49)       | 42 (55)  | 1.1 (0.6–2) | 0.75    | 13 (39)  | 1 (0.4–2.3) | 1       |
| 1236TT            | 8 (8)         | 2 (3)    | 0.3 (0.01–0.6) | 0.2 | 8 (24)  | 3.6 (1–11.5) | 0.05    |
| 1236C             | 135 (67.5)    | 108 (70) | Ref.        |         | 37 (56)  | Ref.        |         |
| 1236T             | 65 (32.5)     | 46 (30)  | 0.9 (0.6–0.4) | 0.65 | 29 (44)  | 1.6 (1–2.9) | 0.1     |
| HWE p             | 0.24          | 0.01     |             |         |          |             |         |
| 3435CC            | 39 (39)       | 30 (39)  | Ref.        |         | 16 (48)  | Ref.        |         |
| 3435CT            | 51 (51)       | 40 (52)  | 1 (0.5–0.9) | 1       | 13 (39)  | 0.6 (0.3–1.4) | 0.3     |
| 3435TT            | 10 (10)       | 7 (9)    | 0.9 (0.3–2.7) | 1 | 4 (12)  | 1 (0.3–3.6) | 1       |
| 3435C             | 129 (64.5)    | 100 (65) | Ref.        |         | 45 (68)  | Ref.        |         |
| 3435T             | 71 (35.5)     | 54 (35)  | 1 (0.6–1.5) | 1       | 21 (32)  | 0.8 (0.5–1.5) | 0.65    |
| HWE p             | 0.25          | 0.32     |             |         |          |             |         |

HWE: Hardy-Weinberg Equilibrium; CD: Crohn disease; UC: ulcerative colitis; OR: odds ratio; N: number; CC: homozygous wild type; CT: heterozygous; TT: homozygous variant.

## Table 5: Distribution of genetic models of MDRI polymorphisms in IBD patients and controls.

| Genotypes/alleles | Control N (%) | CD N (%) | OR (95% CI) | P value | UC N (%) | OR (95% CI) | P value |
|-------------------|---------------|----------|-------------|---------|----------|-------------|---------|
| 1236CC/CT\a        | 92 (92)       | 75 (97.5)| Ref.        |         | 25 (76)  | Ref.        |         |
| 1236TT            | 8 (8)         | 2 (2.5)  | 0.3 (0.06–1.5) | 0.2     | 8 (24)  | 3.7 (1.3–10.7) | 0.03    |
| 1236CC\b          | 43 (43)       | 33 (43)  | Ref.        |         | 12 (36)  | Ref.        |         |
| 1236CT/TT         | 57 (57)       | 44 (57)  | 1 (0.5–1.8) | 1       | 21 (64)  | 1.3 (0.6–2.9) | 0.5    |
| 3435CC/CT\a        | 90 (90)       | 70 (91)  | Ref.        |         | 29 (88)  | Ref.        |         |
| 3435TT            | 10 (10)       | 7 (9)    | 1 (0.3–2.5) | 1       | 4 (12)  | 1.2 (0.4–4.3) | 0.7     |
| 3435CC\b          | 39 (39)       | 30 (39)  | Ref.        |         | 16 (48)  | Ref.        |         |
| 3435CT/TT         | 61 (61)       | 47 (61)  | 1 (0.5–1.8) | 1       | 17 (52)  | 0.7 (0.31–1.5) | 0.42    |

\a Recessive model; \b dominant model; CD: Crohn disease; UC: ulcerative colitis; OR: odds ratio; N: number; CC: homozygous wild type; CT: heterozygous; TT: homozygous variant.
showed an overall protective effect of the variant allele (Table 2). On the other hand, when combining the very few results on GSTM1 and GSTT1 (Table 3), a significant heterogeneity in frequencies of the null genotype distribution in IBD patients was reported (GSTM1 test for heterogeneity: $Q = 28.95; DF = 2; I^2 = 93.1\%; P < 0.0001$; GSTT1 test for heterogeneity: $Q = 61.47; DF = 2; I^2 = 97\%; P < 0.0001$).

### 4. Discussion

In the present case-control study, we investigated the potential influence of MDR1 C1236T, MDR1 C3435T, GSTM1, and GSTT1 polymorphisms on the risk of CD and UC disease. No genotype-phenotype correlation was observed between clinical characteristics of patients and the different genotypes of C1236T and C3435T polymorphisms in MDR1 (data not shown). Consistent with our results, Fischer et al. reported a lack of association between C3435T and IBD phenotype in Hungarian patients [29]. In contrast, Huebner et al. found that CD behavior was influenced by the C3435T SNP [30]. We noted that the null genotype of GSTT1 was higher in CD patients with the stricturing form. In contrast to our findings, Karban et al. reported that neither GSTM1 null nor the GSTT1 null genotypes were found to be associated with CD or UC phenotypes [21]. The frequencies of MDR1 C1236T and MDR1 C3435T in our patients and controls were statically comparable ($P > 0.05$). Similar findings for the C3435T SNP were reported by Wang et al., in a meta-analysis based essentially on Caucasians [31]. Brinar et al. found that the C3435T was associated with the risk of UC, while the heterozygous 3435CT was associated with a protective effect against CD in Croatian population [32]. Furthermore, Juyal et al. have demonstrated that the C1236T was significantly associated with susceptibility to UC, particularly in the earlier age of onset [33]. It is noteworthy that in our study the recessive model of MDR1 C1236T was statistically associated with the risk of UC ($P < 0.03$). The discrepancy between our findings and those studies might be explained not only by...
the difference in minor allele distribution of \textit{MDR1} C1236T and \textit{MDR1} C3435T in our population but also by the relative small sample size of the present study. We have previously reported the existence of linkage disequilibrium between C1236T and C3435T in \textit{MDR1} gene in our population [26]. It is well established that haplotypes consideration is more informative in association studies [34, 35]. However, in this study we were not able to perform haplotypes analysis due to the relative small sample size. Several studies have provided evidence that the C3435T SNP is associated with IBD and the results of our meta-analysis consolidated this variant as a potential risk factor for IBD in different populations. It is noteworthy that a lack of heterogeneity between studies was observed regarding distribution of both \textit{MDR1} polymorphisms. On the other hand, we have interestingly noted that the \textit{GSTT1} null genotype was found to be significantly associated with the risk of both CD (OR: 2.5, \(P = 0.013\)) and UC disease (OR: 3.5, \(P = 0.004\)). Consistent with our finding, Mittal et al. have reported a significant association of \textit{GSTT1} null genotype with susceptibility to CD and UC in Indian population; however, they also found an association of \textit{GSTM1} null genotype with the risk of UC that we could not replicate [23]. Karban et al. showed that \textit{GSTT1} and \textit{GSTM1} were associated with the risk of CD and UC in Israeli population [21]. The interaction between the two genes in our study showed that the combined \textit{GSTM1} null/\textit{GSTT1} null genotype was associated with the risk of UC at the limit of statistical level. Both previously reported studies have shown the association of the double deletion in \textit{GSTM1} and \textit{GSTT1} genes with IBD [21, 23]. A correlation between \textit{GSTs} polymorphisms and IBD has been rarely discussed; more association studies are needed to validate the conclusions.

5. Conclusion

This is the first study to examine the association of \textit{MDR1}, \textit{GSTM1}, and \textit{GSTT1} polymorphisms with the risk of IBD in a sample of the Moroccan population. It follows from the present case-control study that \textit{GSTT1} null genotype and \textit{MDR1} C1236T in the recessive model are associated with the risk of IBD. Crohn’s disease behavior was influenced by the \textit{GSTT1} null genotype. Moreover, the combined null genotype of \textit{GSTT1} and \textit{GSTM1} was associated with the risk of UC with a limited effect.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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