**IL23R and ATG16L1 variants in Moroccan patients with inflammatory bowel disease**

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**Abstract**

**Background:** Inflammatory bowel diseases (IBD) are chronic diseases of the gastrointestinal tract. Although their pathogenesis is unclear, the combination of genetic predisposition and environmental components are believed to be the main cause of these diseases. Recently, many variants in interleukin 23 receptor (IL23R) and autophagy-related 16-like 1 (ATG16L1) genes have been associated with the disease. Our objective was to assess the frequency of ATG16L1 (T300A) and IL23R (L310P) variants in Moroccan IBD (Crohn’s disease and Ulcerative Colitis) patients and to evaluate a possible effect of these variants on disease’s phenotype and clinical course.

**Methods:** 96 Moroccan IBD patients and 114 unrelated volunteers were genotyped for ATG16L1 (T300A) and IL23R (L310P) variants by PCR-restriction fragment length polymorphism.

**Results:** This is the first report on the prevalence of ATG16L1 (T300A) and IL23R (L310P) variants in a Moroccan group. We found that IL23R (L310P) variant conferred a protective effect for crohn’s disease (CD) but not ulcerative colitis (UC) patients. The presence of ATG16L1 (T300A) mutated alleles was associated with CD type but not with disease onset. In addition, the carriage of T300A variant alleles conferred a protective effect in UC.

**Conclusion:** Our results showed that the prevalence of ATG16L1 and IL23R variants was not significantly different between patients and controls. However a possible role of ATG16L1 (T300A) on CD phenotype was suggested.

**Keywords:** IBD, ATG16L1, IL23R, Moroccan population

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**Background**

Inflammatory bowel disease (IBD) is a chronic and multifactorial disease of the gastrointestinal tract. It includes Crohn’s disease (CD), ulcerative colitis (UC) and undetermined colitis. Their etiologies remain complex and unclear involving an inadequately defined relationship between microbial insult, genetic predisposition and altered intestinal barrier permeability [1]. Several genetic studies have attempted to find out more about the molecular pathogenesis of CD and UC.

Genetic variations in genes related to innate and adaptive immunity have been implicated in IBD pathogenesis. Positive correlations were reported for Interleukin 23 receptor (IL23R) [2] and Autophagy related 16-like 1 (ATG16L1) [3,4] genes.

IL-23 is a heterodimeric cytokine produced by activated macrophages and dendritic cells. It consists of two subunits, a p40 subunit, shared with the IL-12, and a specific IL-23 subunit called p19 [5,6]. Studies have shown that IL-23 is involved in the initiation of the innate and adaptive immune activation that characterizes IBD. It binds a complex of IL-23R and IL-12Rβ subunits. IL-23R is predominantly expressed on activated/memory T cells, T-cell clones, natural killer’s (NK) cells and, at low levels, in monocytes, macrophages, and dendritic cell populations [7,8]. Recent studies have shown the association of some single nucleotide polymorphisms (SNPs) in the IL-23R gene with chronic inflammatory diseases especially IBD (CD and UC). The variant L310P of IL23R gene (more frequent in controls) was reported to confer a strong protection against CD [2]. In Ulcerative colitis, the effect of this mutation seems to be insignificant [9]. In addition, Lin Z

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et al. suggested the role of IL23R (L310P) as a protective polymorphism in UC females [10]. Several studies have established an association between ATG16L1 and IBD in various populations. The ATG16L1 gene plays a key role in autophagy pathways. It encodes a protein widely expressed in intestinal epithelial cells, lymphocytes and macrophages and mediates resistance to intracellular pathogens such as bacteria and viral particles [11]. Hampe at al. reported an association between the T300A (c898G > A) polymorphism and Crohn’s disease [3]. Subsequent replication studies revealed divergent results.

No data were available on the frequency of the ATG16L1 and IL23R variants in the Moroccan population. Hence, we aimed to examine the association between IL23R (L310P) and ATG16L1 (T300A) polymorphisms and inflammatory bowel disease (Crohn’s disease and Ulcerative colitis) in a cohort of Moroccan patients.

Methods
Patients and controls
In this study, a group of 96 Moroccan unrelated IBD patients were recruited at the gastroenterology department of Averroes Hospital, Casablanca, Morocco. The control group included 114 unrelated Moroccan volunteers (blood donors) with no discernable symptoms suggestive of IBD. The diagnosis of CD or UC was based on established clinical, radiological, endoscopic, and histopathology criteria.

Demographic and clinical characteristics were obtained from the participants through a detailed questionnaire. CD phenotype was stratified by age at diagnosis, location and disease’s behaviour according to the Montreal classification [12]. For UC patients, anatomic location was subgrouped using the Paris classification as being ulcerative proctitis (E1), left-sided UC (E2), and extensive UC (E3) [13].

Differences in the frequency of disease characteristics such as age at diagnosis, gender, extra-intestinal manifestations, similar familial cases, and antecedents like appendectomy and smoking were also assessed. The study was approved by the medical school of Casablanca ethical committee. A written informed consent was obtained from all participants or their guardians. Both IBD patients and control group are originated from the different regions of Morocco and confirmed the Moroccan origin of their parents and grandparents.

Genotyping methods
Genomic DNA was isolated from whole blood samples by salting-out method [6]. DNA amount and quality were measured by spectrophotometry. IL23R and ATG16L1 variants genotyping was performed using polymerase chain reaction (PCR) restriction fragment length polymorphism analysis (RFLP) as described respectively by Lin et al. and Csöngéi et al. [10,14].

Reactions were performed in a final volume of 25 μl. PCR products were cleaved with Hph I (L310P) and Lwe I (T300A) (New England Biolabs Ipswich, UK) and electrophoresed on a 3% agarose gel in the presence of a molecular weight marker ladder 100 (New England Biolabs Ipswich, UK). After staining with ethidium bromide, Ultraviolet was used on a transilluminator for reading the gel.

Statistical analysis
Statistical analysis was performed using MedCalc statistical software version 11.6. The Hardy-Weinberg equilibrium test was performed separately for patients and controls to measure the distribution of polymorphisms. The association between IBD (CD and UC) and IL23R (L310P) ATG16L1 (T300A) genotypes was determined by Fisher’s exact test (Odds Ratio with Confidence interval (CI) at 95%). The χ2 test or Fisher test was used to correlate the IL23R and ATG16L1 polymorphisms and clinical parameters. The P value (<0.05) was considered statistically significant in all variables.

Results
Epidemiologic data
One hundred fourteen participants from the general population were genotyped for ATG16L1 (T300A) and IL23R (L310P) along with 69 Crohn’s disease patients (25 women and 44 men) and 30 UC patients (14 women and 16 men). The average age of diagnosis was 24.17 ± 2.48 for CD patients and 35.37 ± 5 for UC patients. For control group, epidemiological and clinical data are shown in Additional file 1: Table S1.

Genetic and clinical correlations
Statistical analysis of the distribution of SNPs studied showed that allele frequencies were conformed to Hardy-Weinberg expectations (=1.14, P = 0.57; =0.017, P = 0.99) (=0.03, P = 0.86; =0.017, P = 0.99) for T300A (ATG16L1) and L310P (IL23R) in CD patients and controls respectively.

Correlation between demographic and clinical characteristics according to ATG16L1 and IL23R genotypes (Tables 1 and 2) revealed a positive association between CD Type and ATG16L1 polymorphism (T300A) with P = 0.03 (Table 1). However, no genotype-phenotype correlation was noticed for the IL23R SNP.

Case–control studies were carried out for the selected polymorphisms. The genotypic and allelic frequencies for the T300A and L310P polymorphisms are presented in Tables 3 and 4 respectively.

The non-synonymous polymorphism, rs2241880 (Thr300Ala), located on the ATG16L1 gene, showed no
significantly increased risk of CD among individuals carrying GG genotype or G allele with the respective odds ratio 2.08 (CI: 0.70-6.17, P = 0.19); 1.22 (CI: 0.79-1.86, P = 0.36) (Table 5). In addition, individuals carrying the mutated allele are not protected from the disease. In contrast to the L310P polymorphism in IL23R gene, which confers protection to individuals with the TT genotype and T allele against the development of Crohn's disease, with respective odds
Additionally, our study assessed the association of ATG16L1 (T300A) and IL23R (L310P) polymorphisms with UC. Analysis of distribution of the two polymorphisms showed that allele frequencies were in Hardy-Weinberg equilibrium (=1.76, P = 0.41 and =0.017, P = 0.99) for ATG16L1 and IL23R (=2.9, P = 0.23; =0.017, P = 0.99).

Table 2 Genotypic frequencies according to clinical parameters of the Moroccan CD patients investigated for the L310P polymorphism

| Clinical Parameter | N | IL23R L310P | P value | Chi-square Test |
|-------------------|---|-------------|---------|-----------------|
| Age of onset      |   |            |         |                 |
| <17 years         | 10| 6 (60.0)   | 0.16    | 3.7             |
| 17-40             | 52| 40 (76.9)  |         |                 |
| >40 years         | 7 | 7 (100.0)  |         |                 |
| Sex               |   |            |         |                 |
| Woman             | 25| 19 (76.0)  |         |                 |
| Man               | 44| 34 (77.3)  |         |                 |
| Type              |   |            |         |                 |
| Fistulizing       | 26| 20 (76.9)  |         |                 |
| Non fistulizing   | 24| 21 (87.5)  |         |                 |
| Stenosing         | 12| 9 (75.0)   |         |                 |
| Fistulizingstenosing | 7 | 3 (42.9)   |         |                 |
| Localization      |   |            |         |                 |
| L1                | 19| 16 (84.2)  |         |                 |
| L1 + P            | 2 | 2 (100.0)  |         |                 |
| L2                | 10| 6 (60.0)   |         |                 |
| L2 + P            | 7 | 7 (100.0)  |         |                 |
| L3                | 19| 13 (68.4)  |         |                 |
| L3 + P            | 1 | -          |         |                 |
| L4                | 2 | -          |         |                 |
| L4 + L2           | 4 | 3 (75.0)   |         |                 |
| P                 | 5 | 4 (80.0)   |         |                 |
| SFC Presence      | 4 | 4 (100.0)  | 0.60    | 0.3             |
| Absence           | 65| 49 (75.4)  | 16 (24.6)|                 |
| Smoking Presence  | 28| 22 (78.6)  |         | 1.0             |
| Absence           | 41| 31 (75.6)  |         | 0.0             |
| Appendectomy      |   |            |         |                 |
| Presence          | 9 | 6 (66.7)   |         | 0.73            |
| Absence           | 60| 47 (78.3)  |         | 0.12            |
| EIM Presence      | 39| 33 (84.6)  |         | 0.14            |
| Absence           | 30| 20 (66.7)  |         | 2.14            |
| Surgery Presence  | 29| 20 (69.0)  |         | 0.30            |
| Absence           | 40| 33 (82.5)  |         | 1.1             |

(SFC: Similar familial cases; EIM: Extra intestinal manifestations; N: Total number; CC: wild type IL23R L310P, CT: IL23R L310P heterozygous variant, TT: IL23R L310P homozygous variant).
For both polymorphisms, no genotype-phenotype correlation was observed in UC (Tables 5 and 6).

The genotypic and allelic frequencies did not significantly differ between UC patients and healthy controls for the two polymorphisms (Tables 7 and 8).

Carriers of mutated allele in ATG16L1 gene have a protective effect for UC, with an odds ratio of 0.90 (CI: 0.50-1.61, P = 0.72) (Table 7). While carriers of mutated allele in IL23R gene are not protected from UC, with an OR of 2.10 (CI: 0.92-4.77, P = 0.08) (Table 8).

### Discussion

#### ATG16L1 polymorphism

The association of genes within the autophagy pathway with IBD was observed in several studies. One of the prime candidate genes discovered was the ATG16L1 gene, ATG16L1 is a protein expressed in the colon, leukocytes, intestinal epithelial cells, small intestine, and spleen [15]. A mutation on the gene encoding this protein, located on chromosome 2, has been associated with the onset of ileal CD [16]. It has been shown that ATG16L1 is a key molecule in elucidating the genetic aspects of CD. The findings of associations with variants in ATG16L1 and IBD have prompted further research on understanding the role of the autophagy pathway in disease pathogenesis.

During a genome-wide survey of 19,779 non-synonymous single nucleotide polymorphisms, the (Thr300Ala) variant, located at the N terminus of the WD-repeat domain in ATG16L1, was found to be highly associated with CD by using a haplotype and regression analysis [3]. Subsequent to the initial genome-wide association study, many studies have consistently identified associations between the ATG16L1 (Thr300Ala) variant and CD [17,18]. This finding has been widely replicated in different populations [19-32].

In the present study, we examined the association of ATG16L1 (T300A) genetic variant with CD and UC in Moroccan patients and controls. Upon association analysis, we were not able to establish a significant effect on CD risk in Moroccan IBD cohort. Our result was in concordance with the lack of association reported in a replication study performed in Japan [33]. In addition, Van Limbergen et al. [34] observed that the ATG16L1 variant was found to be highly associated with CD by using a haplotype and regression analysis [3]. Subsequent to the initial genome-wide association study, many studies have consistently identified associations between the ATG16L1 (Thr300Ala) variant and CD [17,18]. This finding has been widely replicated in different populations [19-32].
is associated with susceptibility to adult CD, but not with early-onset disease in a Scottish cohort.

Regarding UC, a protective effect of this polymorphism was identified. At present, it can only be speculated how ATG16L1 T300A variant may confers risk or protection from infection, depending on the nature of the pathogen and the typical duration of infection. The cellular expression of ATG16L1 facilitates bacterial invasion, however the IBD-associated ATG16L1 T300A variant may be protective against bacterial infection.

Messer et al. demonstrated that Intestinal epithelial cells somatically targeted to express the ATG16L1 T300A variant show protection against invasion by Salmonella [23].

### Table 6 Genotypic frequencies according to clinical parameters of the Moroccan UC patients investigated for the L310P polymorphism

| Clinical parameters | N | IL23L310P P value Chi-deux test |
|---------------------|---|---------------------------------|
| Age of onset        |   | CC CT TT                         |
| <17 years           | 21 | 16 (76.2) 4 (19.0) 1 (4.8)       |
| 17-40               | 9  | 5 (55.6) 4 (44.4)                 |
| >40 years           |   |                                 |
| Sex                 |   | CC CT TT                         |
| Woman               | 14 | 11 (78.6) 2 (14.3) 1 (7.1)       |
| Man                 | 16 | 10 (62.5) 6 (37.5)                |
| Localization       |   | CC CT TT                         |
| Left colitis        | 11 | 6 (54.5) 5 (45.5)                 |
| Right colitis       | 13 | 10 (76.9) 2 (15.4) 1 (7.7)       |
| Proctitis           | 4  | 4 (100.0)                        |
| SFC                 |   | CC CT TT                         |
| Presence            | 1  | 1 (100.0)                        |
| Absence             | 29 | 20 (69.0) 8 (27.6) 1 (3.4)       |
| Smoking             |   | CC CT TT                         |
| Presence            | 8  | 6 (75.0) 2 (25.0)                 |
| Absence             | 22 | 15 (68.2) 6 (27.3) 1 (4.5)       |
| Appendectomy        |   | CC CT TT                         |
| Presence            | 30 |                                 |
| Absence             | 30 |                                 |
| EIM                 |   | CC CT TT                         |
| Presence            | 17 | 11 (64.7) 5 (29.4) 1 (5.9)       |
| Absence             | 13 | 10 (76.9) 3 (23.1)                |
| Surgery             |   | CC CT TT                         |
| Presence            | 26 | 17 (65.4) 8 (30.8) 1 (3.8)       |
| Absence             | 4  | 4 (100.0)                        |

(SFC: Similar familial cases; EIM: Extra intestinal manifestations; N: Total number; CC: wild type IL23R L310P, CT: IL23R L310P heterozygous variant, TT: IL23R L310P homozygous variant.)

### Table 7 Genotypic and allelic frequencies for the ATG16L1 of UC patients and controls

| Genotype allele | Case (%) N = 30 | Controls (%) N = 115 | OR (0.95 CI) P value |
|-----------------|-----------------|----------------------|---------------------|
| AA              | 11 (36.7)       | 30 (26.1)            | 1.0                 |
| AG              | 15 (50.0)       | 76 (66.1)            | 0.54 (0.22-1.30)    |
| GG              | 4 (13.3)        | 9 (7.8)              | 1.21 (0.31-4.75)    |
| A               | 37 (61.7)       | 136 (59.1)           | 1.0                 |
| G               | 23 (38.3)       | 94 (40.9)            | 0.90 (0.50-1.61)    |

(AA: wild type ATG16L1 T300A, AG: ATG16L1 T300A heterozygous variant, GG: ATG16L1 T300A homozygous variant; N: Total number; OR: odd ratio; CI confidence interval; P: (P < 0.05)).

### IL23R polymorphism

The IL23R gene is another potential candidate gene for CD risk [2,35]. IL-23R interacts with IL-23, which is a cytokine that orchestrates intestinal inflammation via multiple pathways. It regulates the activity of immune cells and plays an important role in the inflammatory response against infection by bacteria and viruses [36]. The IL-23-IL17 axis is a key pathogenic mechanism that mediates the development and progress of inflammation by Th-17 cells. The role of the IL23-IL17 axis in IBD was supported in human patients and animal models of colitis [37-39]. Similarly, several studies have pinpointed IL23 receptor as a key pathway in the pathogenesis of inflammatory bowel disease. It was confirmed by the genetic association of several SNPs throughout the IL23R gene with CD and UC [21,22,24-27,30,32,40-43].

It was hypothesized that IL23R gene variants have a differential effect on Th17 cells with increased Th17 cytokine secretion in patients with CD-associated IL23R variants and decreased cytokine secretion in patients with CD-protective IL23R variants [44].

In the present study, carriage of the variant allele was associated with a protective effect for CD patients, similarly to previously reported studies [45,46]. We further analyzed whether the risk factor in the IL23R gene was also shared by UC patients and did not detect a significant association. Our subgroup analyses are likely

### Table 8 Genotypic and allelic frequencies for the IL23R of UC patients and controls

| Genotype allele | Case (%) N = 30 | Controls (%) N = 115 | OR (0.95 CI) P value |
|-----------------|-----------------|----------------------|---------------------|
| CC              | 21 (70.0)       | 98 (85.2)            | 1.0                 |
| CT              | 8 (26.7)        | 14 (12.2)            | 2.67 (0.99-7.16)    |
| TT              | 1 (3.3)         | 3 (2.6)              | 1.56 (0.15-15.70)   |
| C               | 50 (83.3)       | 210 (91.3)           | 1.0                 |
| T               | 10 (16.7)       | 20 (8.7)             | 2.10 (0.92-4.77)    |

(CC: wild type IL23R L310P, CT: IL23R L310P heterozygous variant, TT: IL23R L310P homozygous variant; N: Total number; OR: odd ratio; CI confidence interval; P: (P < 0.05)).
underpowered for revealing a genotype–phenotype relationship. This result confirms previous studies on Italian [47] and North American populations [42].

Conclusion
In summary, the present study seems to indicate that ATG16L1 plays an important role in CD behaviour and confers protection for UC. In addition, IL23R gene showed a protective effect for individuals with the TT genotype and T allele against the development of Crohn’s disease.

Therefore, our results could reinforce the notion of a different relevance of ATG16L1 and IL23R in the pathogenesis of IBD in patients of different ethnic origin, with a limited role in the Moroccan population. Due to small sample size, an association cannot be ruled out. Further studies in larger groups would be required to confirm these findings.

Additional file

Additional file 1: Table S1. Clinical and epidemiological parameters of control group.

Competing interest
The authors declare that they have no competing interests.

Authors’ contribution
NS and NS carried out the molecular genetic studies, recruited the patients and drafted the manuscript. BD performed the statistical analysis. WB participated in the design of the study and the recruitment of patients. SN conceived the study, participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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