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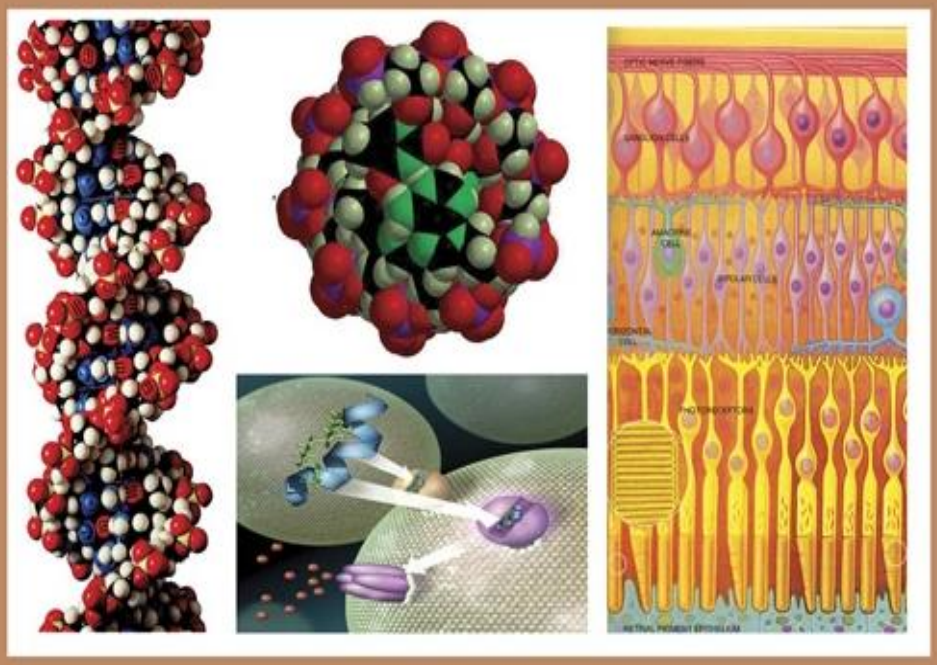

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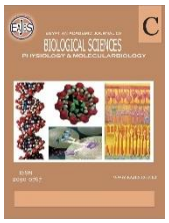

Characterization of ERAP1 rs30187 and rs10050860 Polymorphisms and Their Association with Ankylosing Spondylitis in The Algerian Population Association of ERAP1 in Algeria

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ABSTRACT

Ankylosing spondylitis (AS) is chronic inflammatory rheumatism. The Endoplasmic Reticulum Aminopeptidase (ERAP1) gene is considered the second genetic factor associated with (AS) after HLA-B27. The aim of this study was to assess the role of ERAP1 rs30187 and rs10050860 polymorphisms in susceptibility to AS for the first time in the Algerian population. A total of one hundred sixteen controls and eighty-one AS cases were included in the present study. ERAP1 rs30187 and rs10050860 variants were determined by using the real-time polymerase chain reaction method. Differences in allele and genotype distribution between the cases and controls were tested with adjustment for age. A stratification of case and control groups by HLAB27, age (≤30 or >30), gender (male and female) and clinical characteristics were also performed. Statistical analyses were done using SPSS21.0. No statistically significant association was observed between ERAP1 rs30187 and rs10050860 polymorphisms and AS risk ($p<0.025$). However, stratification by age and gender showed that the minor allele of rs30187 reduces the risk of developing AS in women with age >30 (OR=0.13[0.04-0.39], $p = 6.10^{-5}$), TT genotype (OR=0.09[0.01-0.6], $p=5.10^{-3}$) and dominant model (TT+CT) (OR=0.14[0.03-0.6], $p= 4.10^{-3}$) in a sample of the Algerian population. Indeed, in our study, ERAP1 rs10050860 polymorphism did not predispose us to AS in our population. For the first time, the allelic and genotypic frequencies of ERAP1gene polymorphisms in the Algerian population. This work enriches the library of information about the ERAP1 gene.

INTRODUCTION

AS is the second most frequent chronic inflammatory rheumatism after rheumatoid arthritis. AS multifactorial disease, the etiology of Ankylosing Spondylitis (AS) is influenced by genetic, epigenetic and environmental factors.

A strong genetic predisposition has been shown in more than 90% (Robinson & Brown, 2014). Currently, only 24.4% of the overall genetic risk of AS has been explained(Cortes & Brown, 2011). More than 90% of AS patients are positive for HLA-B27, which has an attributable risk of less than 50% of the total risk for AS (Brown *et al.*, 1997, Jaakkola *et al.*, 2004). Then, the 10% of AS patients with HLA-B*27 negative reflects more other genes non–HLA-B*27.

GWAS results revealed only a few candidate genes in AS, such as Endoplasmic Reticulum Aminopeptidase genes (ERAP1 and ERAP2) (Wellcome Trust Case Control Consortium *et al.*, 2007), Interleukin-23 Receptor (IL- 23R)(Wellcome Trust Case Control Consortium *et al.*, 2007, Australo-Anglo-American Spondyloarthritis Consortium (TASC) *et al.*, 2010), Runt-related transcription factor 3 (RUNX3)(Apel *et al.*, 2013, Cortes *et al.*, 2013), and Anthrax toxin receptor 2 (ANTXR2)(Australo-Anglo-American Spondyloarthritis Consortium (TASC) *et al.*, 2010).

AS and ERAP1 association was first discovered in 2007(Wellcome Trust Case Control Consortium *et al.*, 2007). Further studies showed that this association was only found to be authentic in HLA-B*27 positive subjects (B. Chen, Li, & Xu, 2013). In Caucasians, ERAP1 confers the second greatest genetic connection with AS risk after HLA-B27, with a contribution risk of 26 % (Wellcome Trust Case Control Consortium *et al.*, 2007, Haroon & Inman, 2010). One of the most important examples of genetic synergy in polygenic disease is HLA-B*27 and ERAP1(Keidel, Chen, Pointon, & Wordsworth, 2013). This suggests that HLA-B*27 and ERAP1 act together in the pathogenesis of AS (Haroon & Inman, 2010).

ERAP1 gene, located on chromosome 5q15, belongs to the M1-aminopeptidase family. It was considered a functional candidate gene in AS due to its two main functions. The first major role is to adjust peptide precursors to the optimal length of nine amino acids for MHC class I binding and presentation (Yan *et al.*, 2006). This function is accomplished in collaboration with the second member of the ERAP2 aminopeptidase family (aminopeptidase 2) (Yan *et al.*, 2006, Reeves, Elliott, James, & Edwards, 2014). The second function is to cleave cytokine receptors (IL-1, IL-6 and TNF) on the cell surface (Cui *et al.*, 2002). Genetic variations may interfere with ERAP1 function, leading to pro-inflammatory effects and an imbalance in the immune response.

ERAP1 is a polymorphic gene with several common missense variants (Saric *et al.*, 2002). Five SNPs (rs27044, rs30187, rs10050860, rs17482078 and rs2287987) have been identified as being associated with AS in several Caucasian and Asian studies (Wellcome Trust Case Control Consortium *et al.*, 2007). The risk conferred by these polymorphisms is related to the susceptibility and not the severity of the disease (Keidel *et al.*, 2013).

The rs30187 polymorphism, at position 1583 in exon 11, induces a substitution from C to T (R528AK), and several studies have shown that R528 reduces the activity of the EARP1 (Goto, Tanji, Hattori, & Tsujimoto, 2008, Australo-Anglo-American Spondyloarthritis Consortium (TASC) *et al.*, 2010). Its localization near the entry of the substrate pocket could affect substrate affinity with the enzyme and reduce ERAP1 activity (Wang *et al.*, 2017).

In a case-control study, one haplotype, rs30187-rs10050860-rs27044 (AGG), was found to be one of the most significantly associated with AS (Maksymowych *et al.*, 2009). In other studies, the homozygous status of rs30187-10050860 (GA) seems to decrease 3-4 times the AS risk (Evans *et al.*, 2011). However, according to a case-control on cohorts of France and Belgium populations, rs30187-rs10050860-rs17482078 (GAA) is an AS-protective haplotype, while rs30187-

rs10050860-rs17482078 (AGG) is an AS-risk haplotype (Kadi *et al.*, 2013).

This study aimed to determine the association of the ERAP1 gene SNPs (rs30187 and rs10050860) with AS in the Algerian population. We also analyzed the relation of these AS-associated ERAP1 polymorphisms with HLA-B27, age, gender, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and C-reactive protein (CRP).

MATERIALS AND METHODS

Study Population:

In total, one hundred ninety-seven subjects were enrolled in this case-control study: One hundred sixteen healthy controls and eighty-one patients with AS. Both the case and control groups are unrelated and collected from West Algeria. The AS group was recruited from the Hospital-University Center of Oran (CHUO, Oran, Algeria). AS Patients were diagnosed with AS according to the Amor and the European Spondyloarthropathy Study Group (ESSG) (Amor et al., 1991). The healthy group had no history of AS or chronic disease. Individuals involved in this study signed informed consent, giving them consent to participate in a genetic study.

Stratification:

We stratified our genotyping results of the two ERAP1 gene SNPs according to the HLAB27 status: HLA B27 negative (HLA-B27-) and HLA B27 positive (HLA-B27 +). For age adjustment, two groups were set as follows: under 30 years and over 30 years, as the first symptoms appear in 80% of cases before the age of 30 (Feldtkeller, Khan, van der Heijde, van der Linden, & Braun, 2003). The BASDAI and BASFI were defined on a scale of 0 to 10. When the score is greater than or equal to 4, the disease is regarded as active.

Genotyping of ERAP1 SNP:

Molecular genotyping of SNPs was performed using the real-time polymerase chain reaction method TaqMan SNP genotyping assay (ERAP1 rs30187 and rs10050860) ID: C_3056885_10, C_3056876_10 respectively (Applied Biosystems Foster City, CA, USA). On qTOWER³ real-time polymerase chain reaction (PCR) machine (Analytik Jena, Germany). A 20 µL PCR reaction contained 1X TaqMan genotyping master mix (Applied Biosystems Foster City, CA, USA), 1X SNP genotyping assay mix, and 20 ng DNA. PCR cycling parameters included pre-denaturation at 60°C for 30 sec, denaturation at 95°C for 10 sec, followed by 50 cycles of denaturation at 95°C for 15 sec each, and finally annealing/extension at 60°C for 90 sec. The PCR products were measured at 60°C for 3 sec, which is proportional to the level of the fluorescence VIC and FAM. Appropriate negative control samples were used.

Statistical Analysis:

The statistical description of continuous variables was indicated by a mean and standard error (SE). A Hardy-Weinberg equilibrium deviation test (HWE) was performed for each polymorphism within the group of controls. The comparisons of the distribution of demographic variables (age, gender) between cases and controls and the polymorphism frequencies comparison between cases and controls were analyzed by Pearson's chi-square ($\chi 2$) test. The p values were considered statistically significant when $p < 0.05$. The Bonferroni correction threshold for the significance of association at 0.025 was mentioned considering the number of tests performed. Odds ratio (OR) and 95% confidence intervals (95% CI) were used for estimating the risk. The Statistical Package for Social Sciences (SPSS) software version 21.0for Windows (SPSS Inc, Chicago, IL) was used to perform multivariate stratification analysis on age at diagnosis (> 30 years), gender (male/female), HLA-B*27 status (presence or absence), and AS clinical characteristics (including BASDAI, BASFI, and CRP).

To test Linkage disequilibrium between ERAP1 rs30187 and rs10050860 polymorphisms, we used THESIAS 3.1 software to determine the haplotypes and to

analyze their distribution between case and control groups.

RESULTS

Cohort Characteristics:

Cases and controls characteristics are given in Table 1. In the AS and healthy control groups, there were 42 (52 %) and 7 (6 %) who were HLA-B27 positive ($p= 10^{-6}$). For the clinical syndromes of patients with AS, 42% of patients were diagnosed with uveitis, 63% with peripheral arthritis and the CRP level was higher in patients with AS (73%).

Table 1: Demographic and clinical characteristics of AS patients and controls.

Subject characteristics	AS patients N=81 (%)	Healthy control N = 116 (%)
Gender*		
Female, (n)	44(54)	68(59)
Male, (n)	37(46)	48(41)
Age* (mean ± SE), years	39.56 ± 1.6	28.85 ± 0.99
≤30, n (%)	25(31)	83(72)
>30, n (%)	56(69)	33(28)
HLA-B27*		
HLA-B27+, n (%)	42 (52)	7(6)
HLA-B27−, n (%)	39(48)	109(94)
Family history		
Presence, n (%)	59(73)	
AS forms		
Axial form, n (%)	22(27)	
Peripheral form, n (%)	8(10)	
Mixt form, n (%)	51(63)	
Clinical features		
Age of onset (mean ± SE), years	31.40 ± 1.6	
Disease duration (mean ± SE), years	8.61 ± 0.9	
Diagnosis delay (mean ± SE), years	4.16 ± 0.7	
Clinical syndromes		
Uveitis, n (%)	34 (42)	
Peripheralarthritis, n (%)	51 (63)	
Deformation (kyphosis), n (%)	14 (17)	
Laboratory test		
BASDAI (mean ± SE), cm 3.6 ± 0.2	3.6 ± 0.2	
BASFI (mean ± SE), cm 3.9 ± 0.25	3.9 ± 0.25	
SGOT (mean ± SE), UI 22.74 ± 1.87	22.74 ± 1.87	
SGPT (mean ± SE), UI 23.24 ± 2.3	23.24 ± 2.3	
ESR (mean ± SE), mm/hr 35.95 ± 2.4	35.95 ± 2.4	
CRP >6 mg/L, n (%)	28(56)	
Medication history		
NSAIDs use, n (%) 65 (80)	65 (80)	
NSAIDssensibility, n (%) 55 (84)	55 (84)	
DMARDs use, n (%)	35 (43)	

The data are presented as the mean ± standard error; n, number; %, frequency; *p < .05 considered statistically significant. AS, ankylosing spondylitis; HLA-B27, human leukocyte antigen-B27; BASDAI, bath ankylosing spondylitis disease activity index; BASFI, bath ankylosing spondylitis functional index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SGOT, serum glutamooxaloacetate transferase; SGPT, serum glutamopyruvate transferase; NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease-modifying anti-rheumatic drugs.

ERAP 1 rs30187 and rs10050860 Polymorphisms:

The distribution of genotypes for ERAP1 gene polymorphisms K528R (rs30187) and D575N (rs10050860) showed a Hardy Weinberg's equilibrium in the control group ($p > 0.05$).

Table 2 shows the frequency of ERAP1 polymorphisms (rs30187, rs10050860) in cases and controls. The

results of this study suggested that the genotype TT of rs30187 and the T allele of rs10050860 SNPs of the ERAP1 gene may have a protective effect on AS (OR= 0.49[0.27-0.89], p=0.04), (OR= 0.63[0.40-0.99] p=0.04), respectively, even though, there is no significant distribution after Bonferroni test (Table 2).

Table 2: Allele and genotype frequencies of ERAP1 rs30187 and rs10050860 SNPs in AS patients and controls and related association analyses.

ERAP1 SNPs	Genotypes	AS patients N= 81(%)	Controls N= 116(%)	OR 95% [CI]	*P* value
rs30187	CC[b]	23 (28)	36 (31)	-	1
	CT	21 (26)	46 (40)	-	-
	TT	37 (46)	34 (29)	0.49 [0.27-0.89]	0.04
	CT+TT	58 (72)	80 (69)	-	NS
	Alleles C[b]	67 (41)	118 (51)		1
	T	95 (59)	114 (49)	-	NS
rs10050860	CC[b]	46 (57)	74 (64)		1
	CT	16 (20)	28 (24)		
	TT	19 (23)	14 (12)	-	NS
	CT+TT	35 (43)	42 (36)	-	NS
	Alleles C[b]	108 (67)	176 (76)	-	1
	T	54 (33)	56 (24)	0.63[0.40-0.99]	0.04

The values are presented as genotypes and alleles number (N) and frequency in percentage (%). p, significance; OR, odds ratio; CI, 95% confidence interval. Bold p values mean a significant association with p <0.025 and OR > 1 [CI 95%]. No significant (NS). [b]Reference category.

Stratifications:

Stratification by gender and age was established to study their effects (results not shown). Firstly, there was a significant difference in allelic and genotypic distribution between cases and controls in the female group for rs30187 T allele (OR= 0.38[0.21-0.67], p= 6.10^{-4}) and for rs30187 TT genotype (OR = 0.25 [0.11-0.57], p= 3.10^{-3}) (Table 3).

Table 3: Distribution of allele and genotype frequencies for rs30187 after gender stratification

	Woman group		Statistical analysis	
rs30187	Patients N=44(%)	Controls N=68(%)	OR 95% [CI]	p value
CC[b]	9 (20)	24 (35)	-	1
CT	10 (23)	27 (40)	-	-
TT	25 (57)	17 (25)	**0.25 [0.11- 0.57]**	**3.10^{-3}**
CT+TT	34 (77)	44 (65)	Ns	NS
C[b]	28 (31)	75 (55)		1
T	60 (69)	61 (45)	**0.38[0.21- 0.67]**	**6.10^{-4}**

The values are presented as genotypes and alleles number (N) and frequency in percentage (%). p, significance; OR, odds ratio; CI, 95% confidence interval. Bold p values mean a significant association with p <0.025 and OR > 1 [CI 95%]. No significant (NS). [b]Reference category.

Secondly, a significant allelic and genotype difference was also shown in the group of age >30 years for rs30187 T allele (OR = 0.43[0.23-0.80], p= 7.10^{-3}) and rs30187 (TT+CT) genotypes (OR= 0.39 [0.16 - 0.98], p= 0.04) (Table 4).

Table 4: Distribution of allele and genotype frequencies for rs30187 after age stratification

	Age >30 years old group		Statistical analysis	
rs30187	**Patients N= 55(%)**	**Controls N=34(%)**	**OR 95% [CI]**	***P* value**
CC[b]	13 (24)	15 (44)	-	1
CT	16 (29)	10 (29)	-	-
TT	26 (47)	9 (26)	-	Ns
CT+TT	42 (76)	19 (56)	0.39[0.16-0.98]	0.04
C[b]	42 (38)	40 (59)	-	1
T	68 (62)	28 (41)	**0.43[0.23-0.80]**	**7.10^{-3}**

The values are presented as genotypes and alleles number (N) and frequency in percentage (%). p, significance; OR, odds ratio; CI, 95% confidence interval. Bold p values mean a significant association with p <0.025 and OR > 1 [CI 95%]. No significant (NS). [b]Reference category.

Then, we combined gender and age stratification and the results (Table 3) showed a significant association between allelic and genotypes frequencies of rs30187 and the AS susceptibility in women with age >30 years (T allele (OR = 0.13[0.04-0.39], p = 6.10^{-5}), TT genotype (OR =0.09 [0.01-0.6], p =5.10^{-3}) and (TT+CT) genotypes (OR = 0.14 [0.03-0.6], p= 4.10^{-3}) (results not shown).We also stratified patients and controls according to the presence and absence of the HLA-B*27 alleles to investigate the interaction between ERAP1 SNPs and HLA-B*27. The results of this exploratory analysis showed no significant difference (results not shown).

In addition, genotypes of rs30187 and rs10050860 SNPs were not associated with demographic (results not shown) and clinical data of AS patients (Table 5).

Table 5: rs30187 allele and genotype distributions considering clinical characteristics

	BASDAI		BASFI		CRP	
Genotypes	**Positive N= 32(%)**	**Negative N= 44(%)**	**Positive N=34(%)**	**Negative N= 43(%)**	**Positive N= 37(%)**	**Negative N= 22(%)**
CC[b]	8 (25)	13 (30)	9 (26)	12 (28)	9 (24)	7 (32)
CT	10 (31)	10 (23)	12 (35)	8 (19)	9 (24)	5 (23)
TT	14 (44)	21 (48)	13 (38)	23 (54)	19 (51)	10 (45)
TT+CT	24 (75)	31 (70)	25 (74)	31 (72)	28 (76)	15 (68)
Alleles						
C[b]	26 (41)	36 (41)	38 (56)	54 (63)	27 (48)	19 (43)
T	38 (59)	52 (59)	30 (44)	32 (37)	29 (62)	25 (57)
Statistical analysis	OR95%[CI] *P* value		OR 95%[CI] *P* value		OR 95% [CI] *P* value	
TT	NS		NS		NS	
TT+CT	NS		NS		NS	
T	NS		NS		NS	

The values are presented as genotypes and alleles number (N) and frequency in percentage (%). p, significance; OR, odds ratio; CI, 95% confidence interval. Bold p values mean a significant association with p <0.025 and OR > 1 [CI 95%]. No significant (NS). [b]Reference category.

Haplotype Analysis:

Four haplotypes from ERAP1 rs30187- rs10050860 polymorphisms (TC, TT, CT, CC) were investigated with a comparison of distribution between case and control groups. No one of them showed disease genetic associations (results not shown).

DISCUSSION

We conducted a case-control study to test the association of rs30187 and rs10050860 SNPs with AS already described in several populations of different ethnicities. To our knowledge, this investigation was the first replication study evaluating ERAP1 gene polymorphisms in ankylosing spondylitis in an Algerian population.

The rs30187 Polymorphism:

The T allele of rs30187 SNP was reported as a minor allele in this population (MAF <50%). This result was found similar to those reported on Iran, France, Belgium, Turkey and East Asia populations (Mahmoudi *et al.*, 2012, C. Chen & Zhang, 2015, Gao et al., 2020).

According to Table 2, rs30187 showed a protected effect for AS in the Algerian population, there is no significant distribution after Bonferroni test (Table 2). Two studies on the Turkish and Hungarian populations are concordant with our results (Cinar *et al.*, 2013). However, in Iran, Chinese GWAS and recent meta-analysis, including 26 case-control studies with 31 cohorts (thirteen studies were carried out on Europeans and the other 13 studies were carried out on Asians) showed that rs30187 is significantly associated with an increased risk of AS, especially on Caucasians population(Mahmoudi *et al.*, 2012, Lin *et al.*, 2011, Gao *et al.*, 2020).

The rs10050860 Polymorphism:

For rs10050860 SNP, the T allele represented the minor allele, as demonstrated in Belgian, Portuguese, East Asian and Iranian populations (Kadi *et al.*, 2013, Gao *et al.*, 2020, Lee & Song, 2016, Babaie *et al.*, 2020,).

The protective effect of the minor T allele does not remain after correction for multiple testing. Our study suggests that this polymorphism would not affect the occurrence of AS in the population of Western Algeria. This result appears to agree with the French and Turkish populations (Kadi *et al.*, 2013, C. Chen & Zhang, 2015). However, in a meta-analysis of the East Asian population and another one published in 2016 that included European and Asian patients, a significant association has been found(Gao *et al.*, 2020).

Gender and Sex Stratifications:

Stratification by gender, a protective association with T allele of rs30187 (OR = 0.25 [0.11- 0.57], $p = 3.10^{-3}$and with TT genotype (OR = 0.25 [0.11- 0.57], $p = 3.10^{-3}$) was found in female cases compared to the female controls (Table 3). This protective effect could be explained by the role of gender hormones in the immune response and autoimmune diseases, which have been extensively studied, notably estrogen, which plays a protective role in RA (Moulton, 2018).

Age adjustment indicates that AS patients over the age of 30 carrying a T allele for rs30187(OR = 0.43[0.23-0.80], $p = 7.10^{-3}$) are protected from the AS disease (Table 4). Menopause, in general, can alter disease risk and quality of life. It has been found that in women with systemic lupus erythematosus (SLE) disease activity during perimenopause and menopause is decreasing. This has been explained by estrogen, which can shrink the thymus, decreasing the number of T cells and other functions related to the immune system (Andrea Eisenberg, 2019.).

Indeed, after a combination of gender and age factors, there was a significant association between the minor allele of rs30187 and reducing the risk of developing AS in women with age >30 (OR=0.13 [0.04-0.39], $p = 6.10^{-5}$), TT genotype (OR= 0.09 [0.01-0.6], $p = 5.10^{-3}$) and dominant model (TT+CT) (OR=0.14[0.03-0.6], $p= 4.10^{-3}$ (results not shown).

Interaction With the Status of HLAB-27:

Around 80 to 90 percent of populations of AS patients worldwide are positive for HLA-B27 and the prevalence of AS mirrors the prevalence of HLA-B27 in several populations (Gao *et al.,* 2020). However, only 52% of our AS case sample were HLA-B27 positive (Table 1). It has been found that the majority of studies in North African populations estimate the frequency of HLA-B27 between 50 and 60% among SA patients and between 3 and 4% among healthy individuals (Sakly et al., 2009, Atouf et al., 2012, Hamdi et al., 2012, Tayel *et al.,* 2012, Slimani *et al.,* 2021, Dahmani et al., 2018). This suggests the involvement of other genes in the susceptibility of AS.

The predisposition of HLA-B27 to AS was previously found in this population with OR= 14.62 [6.43-33.20] (Dahmani et al., 2018). We have looked at a possible association of both rs30187 and rs10050860 in the presence and absence of HLA-B*27. We observed no relationship between HLA-B*27 positive or HLA-B27 negative and ERAP1 SNPs (rs30187 and10050860) frequencies. A strong interaction between HLA-B*27 positive in cases-controls and the ERAP1 gene rs30187 polymorphism was found in data from the Wellcome Trust Case Control Consortium 2 (WTCCC2) and from the Australian-Anglo-American Spondylo-Arthritis Consortium (TASC) (WTCCC2 P = 0,02 and TASC P = 0,014 respectively) (Evans et al., 2011).

However, in recent meta-analyses of Yanyan Bai and his collaborators no significant association between the minor allele of rs30187 and rs10050860 and AS susceptibility has been found in the HLA-B*27 positive population(Bai et al., 2022).

Clinical Manifestations:

Genetic variables that influence clinical manifestations are not yet well studied in AS. The disease severity of AS may also be associated with genetic characteristics. However, we found no differences in the BASDAI, BASFI, and CRP levels in AS patients with both polymorphisms (Table 5). The first study that investigated the role of rs30187 and BASFI in the Portuguese cohort did not find any association, consistent with our result (Pimentel-Santos *et al.,* 2009). Whereas Szczypiorska and his collaborators found that rs30187 was associated with AS BASFI (Szczypiorska *et al.*, 2011). Moreover, in an Iranian cohort, rs10050860 showed a strong association with the BASFI score (Babaie et al., 2020).

Haplotypes:

Haplotype analysis of the two SNPs of the ERAP1 gene rs30187 and rs10050860 showed any association with AS. However, Evans DM and his collaborators have reported that carrying homozygous rs30187-rs10050860 (GA) decreased 3 to 4 times the risk of AS (Evans *et al.,* 2011).

The present study had some limitations such as the small sample size and the possibility of other polymorphism risk factors not included in the study. Therefore, an expanded study is required by incorporating a large sample and investigating variants in other genes in order to give more evidence of a genetic contribution to the etiology of AS.

Conclusion

To our knowledge, this is the first study describing the effects of ERAP1 polymorphisms implicated in AS susceptibility in the Algerian population. We demonstrated that the rs30187 and rs10050860 polymorphisms of ERAP1 did not associate with the susceptibility risk in this population, even in haplotype forms. However, rs30187 has been found as a protective factor against AS for women over 30 years old.

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ARABIC SUMMARY

توصيف تعدد الأشكال ERAP1 rs30187, rs10050860 وارتباطها بالتهاب الفقار اللاصق في السكان الجزائريين

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التهاب الفقار اللاصق هو التهاب روماتيزمي التهابي مزمن. يعتبر جين الشبكة الإندوبلازمية العامل الوراثي الثاني المرتبط بالتهاب الفقار اللاصق بعد HLA-B27. كان الهدف من هذه الدراسة هو تقييم دور تعدد الأشكال ERAP1 rs30187وrs10050860 في التأثر بـ AS لأول مرة في السكان الجزائريين. تم تضمين ما مجموعه مائة وستة عشر ضوابط وواحد وثمانين حالة AS في هذه الدراسة. تم تحديد متغيرات ERAP1 rs30187 وrs10050860 باستخدام طريقة تفاعل البلمرة المتسلسل في الوقت الفعلي. تم اختبار الفروق في توزيع الأليل والنمط الجيني بين الحالات والضوابط مع التكيف مع العمر. تم إجراء التقسيم الطبقي للحالة ومجموعات المراقبة حسب HLAB27 والعمر (30 أو< 30) والجنس (ذكر وأنثى) والخصائص السريرية. تم إجراء التحليلات الإحصائية باستخدام SPSS21.0. لم يلاحظ أي ارتباط ذي دلالة إحصائية بين ERAP1 rs30187 وrs10050860 تعدد الأشكال وخطر التهاب الفقار اللاصق .(p <0.025) ومع ذلك ، أظهر التقسيم الطبقي حسب العمر والجنس أن الأليل الصغير لـ rs30187 يقلل من خطر الإصابة بالتهاب الفقار اللاصق عند النساء اللائي تزيد أعمارهن عن 30 عامًا [OR = 0.13 [0.04-0.39) ، (p = 6.10-5، النمط الجيني TT (OR = 0.09 [0.01-0.6]، (p = 5.10-3والنموذج السائد [OR = 0.14 [0.03-0.6) (TT + CT) ، p = (4.10-3في عينة من السكان الجزائريين. في الواقع ، في دراستنا ، لم يؤد تعدد الأشكال ERAP1 rs10050860 إلى التهاب الفقار اللاصق في مجتمعنا. تساهم هذه الدراسة في إثراء البيانات المصرفية المتعلقة بجين ERAP1 من خلال الإبلاغ ، لأول مرة ، عن الترددات الأليلية والوراثية لهذه الأشكال الجينية في السكان الجزائريين.

الكلمات المفتاحية ERAP1 , حماية، نساء، فوق 30 سنة، جزائريين