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# Evaluation of HLA-B27 frequency in patients with ankylosing spondylitis, and its relationship with clinical symptoms in Khuzestan province

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## Abstract

**Introduction:** Ankylosing spondylitis (AS) is an autoimmune disease, which causes mild to severe clinical symptoms in patients. Several inherited and acquired factors are involved in the pathogenesis of the disease. Human leukocyte antigen B27 (HLA-B27) is one of the factors, whose expression affects patients' susceptibility to AS.
**Objectives:** In this study, we evaluated HLA-B27 frequency in AS patients of Khuzestan province of Iran.
**Patients and Methods:** The study population (N=114) including patients with AS. Patients were examined and confirmed by a rheumatologist based on New York modified criteria. Clinical information was extracted from patients' documents. Furthermore, general characteristics of the patients and several clinical variables (physio-pathological, self-report, and imaging) were taken into consideration.
**Results:** The results showed that 62.3% of the patients were HLA-B27 positive, while 37.7% of which were HLA-B27 negative. This difference was statistically significant ($P < 0.05$). The disease duration was shown to be almost equal in both groups (i.e., HLA-B27 positive and HLA-B27 negative). According to the results, various clinical symptoms (like ocular complications and peripheral arthritis) were observed in patients, and the complications of which were higher in HLA-B27 negative patients compared to HLA-B27 positive ones ($P < 0.05$). Besides, it was seen that the male patients have shown a higher physio-pathological (using polymerase chain reaction [PCR] technique) report for positive HLA-B27 and a higher magnetic resonance imaging involvement compared with females, whereas the women showed higher disease activity score i.e., higher mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) value.
**Conclusion:** For the AS patients, negative HLA-B27 cases show more progressive involvement sacroiliac joints compared with the positive HLA-B27 cases. More importantly, of hundred percent of patients who responded to anti-tumor necrosis factor (TNF) treatment, 52.6% were positive for the HLA-B27 antigen, and 47.4% were negative for the HLA-B27 antigen. Overall, it can be said that HLA-B27 lonely is not involved in the pathogenesis of AS and environmental factors should be investigated and involved in the disease development.

## Introduction

As a heterogeneous category of rheumatic diseases, spondyloarthropathy (SpA) shows affecting the axial and peripheral skeleton. Ankylosing spondylitis (AS), one type of SpA, acts as an autoimmune disease that implicates spine joints, sacroiliac joints and their adjacent soft tissues like ligaments and tendons (1). Axial spondyloarthritis (axSpA) can be classified to AS (AS) or non-radiographic axSpA. AS exhibit radiographic abnormalities consistent with sacroiliac. However, there are not clear evidences on plain radiography in non-radiographic axSpA. Instead, in AS, the diagnosis is conducted by the evidence of active sacroiliac joints inflammation on magnetic resonance imaging (MRI), by a compound of other findings, or both (2). In fact, it is an autoimmune disease

### Key point

Human leukocyte antigen B27 (HLA-B27) is one of the pathogenesis factors to express the susceptibility of patients to autoimmune ankylosing spondylitis (AS) disease. The current study aimed to investigate the frequency of ankylosing spondylitis in HLA-B27 negative individuals in the southwest of the Iran. In this study we found that 52.6% of patients who responded to anti- anti-tumor necrosis factor treatment were positive for the HLA-B27 antigen and 47.4% of which were negative for the HLA-B27 antigen.

that frequently affects spine, sacroiliac joints, and nearby soft tissues like tendons and ligaments (3). In advanced and acute cases, inflammation leads to fibrosis and calcification, which finally prevents joint flexibility and mobility (4).

Due to the fact that AS is an autoimmune

disease, several genetic and environmental factors are involved in disease development. Genetic changes have been shown to occur in more than 90% of patients (5). One of the most common genetic risk factors is the HLA-B27 genetic allele of the histocompatibility complex (MHC) group, which causes disease in many populations. HLA-B27 is a surface protein, belonging to the MHC class 1 family; its gene is located on the short arm of chromosome number 6 (5,6). This factor is involved in antigens presentation to T lymphocytes, and development of inflammatory responses in AS. HLA-B27 has eight different alleles, and can deliver more than 7500 antigens to lymphocytes (7). When HLA-B27 delivers the antigen to CD8 lymphocytes, it boosts the production of inflammatory cytokines, including interleukin-6 (IL-6) and interferon gamma (IFN-γ) (8).

## Objectives
Considering that HLA-B27 is one of the main pathogenesis factors in AS patients, we decided to study its frequency in patients for the first time, and its relationship with patients' clinical symptoms in Khuzestan province. It should be noted that there is not clear number for the prevalence of AS in the country (Iran) or the province (Khuzestan). However, in some informal institutes like Iranian Society of HLA-B27 Disease it is mentioned to be approximately 150 000 in Iran and 3000-4000 in Khuzestan province. For investigating the disease behavior in the patients, the general characteristics of the patients and several clinical variables (physio-pathological, self-report [BASDAI], and MRI involvement) are taken into consideration.

## Patients and Methods
### Target group
The present investigation was conducted as a retrospective study to investigate the frequency of AS with positive and negative HLA-B27 individuals in the southwest of the Iran (2015 to 2018). Inclusion criteria included patients diagnosed with AS based on New York modified criteria (9). Therefore, patient's age should be between 20 and 40 years, positivity for HLA-B27 using polymerase chain reaction (PCR) test, exhibited clear consciousness; agreed to respond to the required queries; and satisfied to collect the needed data from their medical trends, a proper functional condition, and a high levels of C-reactive protein (CRP). It should be noted that patients with incomplete document and the history of having infectious diseases, cancer, dementia, or spinal tumors were excluded from the study (10).

### Study design
Demographic and clinical information of patients (demographic data including gender, age, onset of symptoms, age of diagnosis, clinical data of peripheral joint involvement and presence of symptoms of sacroiliac involvement, ocular involvement, and drugs used) were extracted from their medical documents. Measurement scales regarding disease activity and MRI imaging were taken into consideration. Along with clinical and imaging (MRI) findings, CRP levels and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) value as scales in determining the ability of the patients for having HLA-B27 have been taken into the consideration. The BASDAI scale was conducted to estimate the AS disease activity. It should be noted that the BASDAI is a validated diagnostic or scale of disease activity test which helps rheumatologists to specify the drug therapy effectiveness, or to establish a newer drug therapy for the AS treatment. The BASDAI composes of a score range between 0 and 10 which is specified by asking six questions of the patient relevant to the significant AS symptoms; (a) spinal pain, (b) fatigue, (c) enthesitis, (d) arthralgia, (e) duration of the morning stiffness, and (f) severity of the morning stiffness (11). According to the BASDAI measurement, (BASDAI scores) ≤2 estimated mild disease activity, 2< (BASDAI scores) <5 estimated moderate disease activity, and 5≤ (BASDAI scores) estimated severe disease activity (10). In addition, PCR test for HLA-B27 detection has been performed based on the Kumar Sah et al investigation (12). In such a way that the DNA from ambient blood containing EDTA anticoagulant of all studied populations by the method of salting out a mixture of 4 μL reaction buffer, 16.9 μL distilled water, 1 μL (50 ng), and 0.1 μL of the polymer was prepared from Taq polymer (0.1 unit/μL). DNA is amplified using specific primers oligonucleotides for exon 3 of the HLA-B27 gene. This multiplication was accomplished by thermal cycle parameters for initial denaturation of PCR at 94°C for five minutes continued by 35 denaturation cycles at 94°C for one minute; primers annealing at 65°C for two minutes and primer extensions at 72°C for one minute and final extension at 72°C for another 10 minutes. Then they are examined for the presence of the HLA-B27 band on 1.5% agarose gel.

Noteworthy is to mention that HLA-B27 positive patients with acute anterior uveitis or chronic back pain are associated with positive family history (PFH) of AS (13). However, it has been illustrated that, even in the absence of HLA-B27 positivity, PFH does not participate in an axSpA diagnosis (13). Since a reliable finding and precise data about the family history of the patients was difficult, this parameter was neglected in the data collection and investigation of this study.

Moreover, pharmacological treatment in accordance with the treatment of AS disease in this study is presented. Improving and maintaining the flexibility of posture normality and spinal, relieve symptoms, decrease complications, and diminish functional restrictions are the objectives of treating AS. The basic principles of pharmacological treatment include nonsteroidal anti-inflammatory medications (NSAIDs) and anti-tumor necrosis factor-α (anti-TNF-α) inhibitors. Further actions involve prescription of sulfasalazine, non-TNFi (non-TNF

inhibitor) biologics, and methotrexate. It should be noted that NSAIDs, mainly cyclooxygenase 2 selective inhibitors, are the first-stage treatment actions for active AS patients (1).

### Statistical analysis

In this study, descriptive statistics containing mean and standard deviation (SD), and frequency and frequency percentage have been utilized. Parametric tests (independent *t* test, paired *t* test and variance analysis) and non-parametric tests (Kruskal-Wallis, Mann-Whitney U) have been conducted to test the research hypotheses. All statistical analysis was carried out with the use of SPSS software and the significance level was set at *P* < 0.05.

### Results

The studied population (N = 114) including patients with AS, who had referred to the rheumatology clinic of Imam Khomeini hospital in Ahvaz during 2015-2018. Patients were examined and confirmed by a rheumatologist based on New York modified criteria. It should be noted that 237 patients of the first 354 participants in this study were excepted from the investigation due to the following criteria; (a) patients with inactive AS (i.e. mean BASDAI < 2 (10); 50 patients) (b) the death of some patients during COVID-19 pandemic and other causes (90 patients), and (c) breaking the progress of the treatment due to the absence of some patients (i.e., 100 patients). In terms of gender, 92 were male (80.7%) and 22 (19.3%) were female. The average age of the selected patients was 30.57 ± 10.43 years, ages ranged from 20 to 40 years. The mean duration of the disease was 27.71 ± 18.0 year. Most patients were married (n = 82; 71.93%) and employed (n = 72; 63.16%). Over 70% of them claimed that their work and life had been influenced by AS. General characteristics corresponding to the selected participants are presented in Table 1.

All symptoms involvement for the AS patients are presented in Table 2. According to this table, sacroiliac joints and inflammatory back pain are observed in all the patients. Then, peripheral arthritis, ocular complications, enthesitis, psoriasis, and dactylitis are the most seen symptoms in the patients. Table 3 depicts the clinical variables according to the pathophysiological proceedings.

According to this table, the mean value of CRP exhibited an abnormal CRP level (i.e., CRP ≥1.0 mg/L) which is corresponding to about 40% of the selected patients. More importantly, it can be seen from this table that the males have shown a higher physio-pathological (i.e., PCR) report for positive HLA-B27 and a higher MRI involvement compared with women, whereas females showed higher disease activity score (i.e., higher mean BASDAI value). This observation is reported in the literature (14) as well. As a comparison between demographic and clinical information of men and women, men experience more severe involvement of their hip and higher BASRI of the spine and modified stoke ankylosing spondylitis spine score (mSASSS) than women (14). It is worth mentioning that BASRI and mSASSS represent respectively Bath Ankylosing Spondylitis Radiology Index and modified Stoke Ankylosing Spondylitis Spine Score. Overall, drastic radiographic malformations, involving ankylosing, are seen for both genders (14). Moreover, the radiological progression of axSpA in men is higher than in women, whereas women show more severe disease activity and more extra-articular symptoms than men (14).

### Evaluation of clinical symptoms in two groups

Based on whether HLA-B27 in the patients was positive or negative, the selected participants were then segregated into two patient classes (Table 4). According to this table, 62.3% of the patients were HLA-B27 positive, while 37.7% of which were HLA-B27 negative. This discrepancy was statistically important (*P* < 0.05). The duration of the AS disease was shown to be almost equal in both groups. As can be seen from this table, ocular complications were higher in the participants with negative HLA-B27 in comparison with those with positive HLA-B27; it was statistically significant (82.9 versus 17.1; *P* < 0.05). In addition, it was shown that the incidence of peripheral arthritis was higher in HLA-B27 negative patients compared to

**Table 1.** General characteristics of the patients with ankylosing spondylitis (N = 114)

| Characteristic | |
| --- | --- |
| Gender, No. (%) | |
| Male | 92 (80.7) |
| Female | 22 (19.3) |
| Age (range: 20-40 years), Mean ± SD | 30.57 ± 10.43 |
| Marital status, No. (%) | |
| Married | 82 (71.93) |
| Single | 32 (28.07) |
| Education, No. (%) | |
| High school or below | 76 (66.67) |
| College or above | 38 (33.33) |
| Employment status, No. (%) | |
| Unemployed | 42 (36.84) |
| Employed (full time) | 72 (63.16) |
| AS duration (year), Mean ± SD | 27.21 ± 18 |

**Table 2.** Distribution of the various symptoms in the ankylosing spondylitis patients

| Symptoms | Involvement (Male/Female) (%) |
| --- | --- |
| Uveitis/ocular complications | 46.74/31.82 |
| Peripheral arthritis | 81.54/72.72 |
| Sacroiliac joints | 100/100 |
| Enthesitis | 32.6/31.82 |
| Dactylitis | 19.56/22.73 |
| Psoriasis | 22.83/27.27 |
| Inflammatory back pain | 100/100 |

**Table 3.** Clinical variables for the selected patients (N = 114)

| Clinical variables | | | | |
|---|---|---|---|---|
| **CRP, mg/dL** | **Mean** | **Range** | **SD** | ***P* value** |
| Male and female | 2.3 | 0–8.19 | 3.4 | > 0.5 |
| **PCR (+ or -)** | **HLA-B27 positive (%)** | **HLA-B27 negative (%)** | | |
| Male | 70.6 | 29.4 | | > 0.5 |
| Female | 62.7 | 37.3 | | > 0.5 |
| **Self-report (using BASDAI)** | **Mean** | **Range** | **SD** | ***P* value** |
| Male | 3.5 | 0–8.3 | 2.01 | <0.05 |
| Female | 4.3 | 0-8.9 | 2.4 | <0.05 |
| **Imaging (using MRI involvement)** | **Fraction (%)** | | | ***P* value** |
| Male (%) | 48.8 | | | > 0.5 |
| Female (%) | 37.4 | | | > 0.5 |

Abbreviations: CRP, C-reactive protein; PCR, polymerase chain reaction; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; MRI, magnetic resonance imaging.

**Table 4.** Relationship between clinical symptoms and HLA-B27

| Variables | HLA-B27 positive | HLA-B27 negative | P value |
|---|---|---|---|
| HLA-B27 (%) | 62.3 | 37.7 | <0.05 |
| Age (mean ± SD) | 31.13 ± 10.60 | 29.65 ± 10.19 | > 0.5 |
| Eye complication (%) | 17.1 | 82.9 | <0.05 |
| Peripheral arthritis (%) | 38.2 | 61.8 | <0.05 |
| Enthesitis (%) | 36.6 | 63.4 | <0.05 |
| Psoriasis (%) | 41.4 | 58.6 | <0.05 |
| Dactylitis (%) | 46.1 | 53.9 | <0.05 |
| Duration of disease (mean ± SD) | 24.82 ± 16.11 | 24.52 ± 20.25 | > 0.5 |
| Gender (Male/Female) (%) | 70.6/62.7 | 29.4/37.3 | > 0.5 |
| MRI involvement (%) | 46.5 | 53.5 | > 0.5 |
| Anti-TNF (Yes/No) (%) | 52.6/68.4 | 47.4/31.6 | > 0.5 |

TNF, tumor necrosis factor.

HLA-B27 positive individuals (61.8 versus 38.2; $P < 0.05$). In addition, other incidences corresponding to the rest symptoms (i.e., enthesitis, psoriasis and dactylitis) have almost similar trend to the previous mentioned symptoms (ocular complications and peripheral arthritis).

Furthermore, this table presents MRI involvement for the two groups. According to this table, MRI involvement for the cases with negative HLA-B27 shows more progressive involvement of sacroiliac joints than the positive HLA-B27 cases. This result is contrary to the statement of Chung et al [15]. However, this can be because, the patients with negative HLA-B27 get the disease signs' more complexly than positive HLA-B27 cases due to other differential diagnosis of negative HLA-B27 with low back pain [16].

According to Table 4, no remarkable relationship between the two groups with regard to taking anti-TNF drugs was detected ($P > 0.05$). Out of hundred percent of people who responded to anti-TNF treatment, 52.6% were positive for HLA-B27 antigen, and 47.4% were negative for it. It should be noted that HLA-B27 antigen has been found to be a predictor for having a positive treatment response on biologics [14]. Overall, of the hundred percent of people who did not respond to drug treatment, 68.4% had the antigen and 31.6% had not it. The presence of this antigen has no significant relationship with drug treatment. This may be due to the presence of enthesitis in the patients (about 31%; presented in Table 2), which is mentioned to be as a barrier in the treatment efficacy [14]. Only the existence of this antigen in people who are positive in the early stages of the disease can detect the presence of the disease.

## Discussion
Ankylosing spondylitis is one of the autoimmune diseases that leads to mild to severe clinical disorders and symptoms in patients. Clinical symptoms vary depending on which organ is involved [17]. In terms of onset age, it had occurred at young ages, which was similar to previous studies [18]. Regarding gender, the results showed that the incidence of disease was higher in HLA-B27 positive men and women compared to HLA-B27 negatives; however, this difference was not statistically remarkable (p-value> 0.05). Nevertheless, in the study of Yang et al [19], disease incidence was higher in HLA-B27 positive men in comparison with HLA-B27 negative individuals.

The seen complications (see Table 4) in the AS patients with positive HLA-B27 can be justified as the following justification [20]; owing to cysteine remnant C67, HLA-B27 does not have suitable folding compared with other HLA alleles (i.e., slower folding compared to other HLA alleles). The mentioned faulty HLA-B27 proteins frequently

accumulate in the endoplasmic reticulum (i.e., ER) and cause the activation of autophagy and the IL-23/IL-17 pathway. Besides, these misfolded proteins have the ability to interfere with the function of ER, leading to ER stress and even triggering the pro-inflammatory endoplasmic reticulum unfolded protein response (ERUPR), which further activates the IL-23/IL-17 pathway (21). For the cases with negative HLA-B27 the following pathogenesis justification can be referenced for the AS disease with several complications (see Table 4) (20); endoplasmic reticulum aminopeptidase 1 (ERAP1) is one of genes located outside of the MHC (i.e., histocompatibility complex) locus. It has been reported that ERAP1 is related to the HLA-B27 negativity. In addition, interactions among ERAP1 and negative HLA-B27 occur gene-to-gene, and correspondingly the presentation of abnormal peptides can be related to the AS progression. On the other hand, ERAP1 variation may decrease the HLA-B27 folding speed by influencing the relative achievable peptide content, as a result enhancing ER stress and AS growth, and leading to further inflammatory processes.

Among women, the disease incidence was higher in HLA-B27 negative cases; this finding was statistically significant (5). In the study of Akassou et al (22), it was shown that the incidence of AS was higher in men compared to women (6). Based on previous studies, it was shown that disease complications are more severe in AS patients with positive HLA-B27 than those with negative HLA-B27. The prognosis and response to treatment in these patients are poor, which are associated with reduced patient survival (23). Accordingly, the study of Yang et al. (19) has shown that ocular and ocular complications were more severe in patients with positive HLA-B27 than negative HLA-B27 ones, which was statistically significant (19). Meanwhile, Pathanapitoon et al indicated that the acute anterior uveitis incidence was higher in patients with positive HLA-B27 (24). However, the results of the present study were contrary to the previous studies. Our study showed that the frequency of ocular complications and peripheral arthritis was higher in AS HLA-B27 negatives in comparison with AS HLA-B27 positives. Considering that the incidence of complications in AS patients with negative HLA-B27 was higher than that in positive HLA-B27 ones, it is possible that environmental factors played an important role in disease progression in the patients under study compared to hereditary factors (18, 25), which requires further studies. Last but not least, Reveille and Arnett (26) have mentioned that in spite of the strong relation between HLA-B27 and AS, only 2–5% of positive HLA-B27 patients develop AS, proposing that other possible factors such as other loci, accidental or environmental factors can participate remarkably in the progression of AS.

## Conclusion
In this study, a population (N=114) of patients with active AS, which was selected with a strict criterion, was investigated during 2015-2018 in Ahvaz, Iran. General characteristics of the patients and several clinical variables (physio-pathological, self-report, and imaging) were taken into consideration. According to the results, various clinical symptoms were observed in the AS patients, and the complications of which were more severe in the patients with negative HLA-B27 than HLA-B27 positive ones. Moreover, it was seen that the men with AS have shown a higher physio-pathological (i.e., PCR) report for positive HLA-B27 and a higher MRI involvement compared with the women with AS, whereas the women showed higher disease activity (i.e., higher mean BASDAI value). Furthermore, MRI involvement for the cases with negative HLA-B27 shows more progressive involvement sacroiliac joints than the positive HLA-B27 cases. Moreover, of the hundred percent of patients who responded to anti-TNF treatment, 52.6% were positive for the HLA-B27 antigen, and 47.4% were negative for the HLA-B27 antigen.

## Limitations of the study
According to the mentioned strict criteria in the Method Section and the financial and geographic limitations, the size of AS disease population (i.e., N=114) from the rheumatology clinic of Imam Khomeini Hospital in Ahvaz may not be a comprehensive nominate for the entire Khuzestan province population. In addition, as the studied period coincide with COVID-19 pandemic, some patients disappeared from the study due to several causes like, not being AS a priority disease, death by COVID-19, and financial priorities. Therefore, investigating the post pandemic symptoms of COVID-19 on the AS diagnosis and treatment can be conducted in the future works. Furthermore, in this study only the BASDAI is conducted as the self-report testing of the patients. Therefore, for having a more comprehensive insight, other self-report criteria (like, BASFI, NRS, BDI-II, and BIS) can be applied in the future works. Finally, having a reliable clear family history about the AS patients can be a good option in better determining the behavior of the AS symptoms and progression.

## Authors' contribution
**Conceptualization:** MD, FN, ER.
**Investigation:** MD
**Methodology:** MD.
**Formal analysis:** MD.
**Visualization:** MD.
**Writing–original draft:** MD
**Writing–review and editing:** MD, FN, ER.
**Supervision:** FN, ER.
**Project administration:** FN.
**Data curation:** FN.

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