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ORIGINAL ARTICLE

High frequencies of HLA-B27 in Chinese patients with suspected of ankylosing spondylitis

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Abstract This study was performed to investigate the frequency of human leukocyte antigen (HLA)-B27 in Chinese patients with suspected of ankylosing spondylitis (AS) and to assess the clinical significance of HLA-B27 typing. A total of 1,016 patients suspected of AS were classified into six groups based on one major AS-related clinical manifestation. HLA-B27 was determined by polymerase chain reaction using sequence-specific primers. The frequency of B27 ranged between 24.3 and 46.7% among the patient groups, significantly higher than in healthy controls (2.4%). In the same group, the frequency of B27 in young (≤40 years) and in male patients was significantly higher than in the old and in female ($P < 0.01$). During a 1-year follow-up, 102 subjects were definitely diagnosed as AS, but only one B27(−) patient. Of the 102 definite patients, 69 (67.6%) definite patients were distributed in group 1 (low back pain and stiffness) with the higher incidence (28.5%) of AS. The incidence of AS in the same group was found with a similar pattern to the frequency of B27, in male and young patients significantly greater, except groups 4 and 6 (peripheral arthritis and alteration of skin). These findings confirm that HLA-B27 is one of sensitive diagnostic tools for early AS and suggest that there was a remarkable clinical significance of HLA-B27 typing in Chinese patients suspected of AS, particularly a young man who presents with low back pain and stiffness for >3 months.

Keywords Human leukocyte antigen · HLA-B27 · Chinese patients · Ankylosing spondylitis (AS)

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Introduction

Ankylosing spondylitis (AS) is a complex, potentially debilitating disease that is insidious in onset, progressing to radiological sacroiliitis over several years [1]. The severely impaired lives with considerable suffering and personal-societal costs may be substantial [2–5].The prevalence of AS is about 0.5–1% [6] and the pathogenesis is poorly understood. Early identification of AS patients who develop early progression is essential because deformed disease, at an early stage can benefit from early intensive treatment.

The association of human leukocyte antigen (HLA)-B27 with AS has been known for more than 36 years; and it remains one of the best examples of a disease association with a hereditary marker [7, 8]. The primary role of HLA-B27 is in diagnosis. Its primary utility in diagnosis comes in the patient, particularly with suspected of AS without classical radiographic features [9]. The demonstration of HLA-B27 positivity can influence both early diagnostic and, ultimately, treatment decisions [10].

The prevalence of HLA-B27 and the association with AS vary markedly in some ethnic and racial groups [11, 12]. Its usefulness differs appreciably among various ethnic/racial groups. The overall clinical usefulness (predictive value) of the HLA-B27 test will be highest in population groups with low general prevalence of HLA-B27 and yet strong disease association [13].

Although there are a large number of studies on the incidence of HLA-B27 in various populations, the frequency of HLA-B27 in patients with suspected of AS has been less analyzed. The aim of this study was to investigate the frequencies of HLA-B27 in Chinese patients with suspected of AS and to assess the clinical significance of HLA-B27 typing.

Materials and methods

Study population

Owing to the lack of validated criteria for the diagnosis of early AS, the subjects presented AS-related clinical manifestation, such as low back pain and stiffness, alternating buttock pain, enthesitis, etc., were chosen as patients suspected of AS. A total of 1,016 patients were recruited from rheumatology outpatient clinics of Union Hospital, Tongji Medical College, Hua-Zhong Science and Technology University between January 2007 and 2008. Furthermore, a group of 167 healthy blood donors, mainly students and recruits, were drawn from universities and the uniformed services. All patients and control subjects originated from throughout China, mostly Han nationality and unrelated to one another. During a 1-year follow-up, patients with confirmed AS fulfilled the 1984 New York modified Criteria [14]. The definite patients was investigated regarding clinical manifestations, sex and age distribution.

For this study, we obtained ethics committee approval and informed consent was also obtained from patients as well as control subjects prior to the participation in the study.

Patients with suspected of AS grouping

On the basis of one major AS-related clinical manifestation, the patients were divided into the following groups:

Group 1: low back pain and stiffness for >3 months
Group 2: alternating buttock pain
Group 3: enthesitis
Group 4: peripheral arthritis
Group 5: ocular inflammation
Group 6: alteration of skin.

Demographic characteristics of patients suspected of AS and healthy controls are given in Table 1.

HLA-B27 typing

Genomic DNA was extracted from whole blood samples by a standard salting-out method [15]. The HLA-B27 was typed using polymerase chain reaction-sequence-specific primer designed by Voorter et al. [16] and Zino et al. [17].

Table 1 Demographic characteristics of patients suspected of AS and healthy controls

Group	*n* (%)	Gender ratio (M:F)	Age (years; mean ± SD)
Total number	1,016	1.2.	38.9 ± 9.1
1. Low back pain and stiffness	242 (23.8)	1.1.	31.3 ± 10.2
2. Alternating buttock pain	263 (25.8)	1.3	35.7 ± 11.6
3. Enthesitis	79 (7.8)	1.7	33.4 ± 10.7
4. Peripheral arthritis	326 (32.1)	1.1	39.7 ± 9.3
5. Ocular inflammation	69 (6.8)	1.7	38.9 ± 13.4
6. Alteration of skin	37 (3.6)	1.3.	36.0 ± 14.1
Healthy controls	167	1.4	25.1 ± 8.6

Statistical analysis

The frequencies of HLA-B27 were determined by direct count. Statistical evaluation was done using χ^2 tests, Fisher's exact test, where appropriate. The level of significance was set at 0.05.

Results

A total of 1,016 patients were studied, 456 women and 560 men. According to their different clinical manifestations, the patients were divided into six groups. Among 1,016 patients, the frequency of HLA-B27 was 36.0% (366 cases). In the groups studied, the frequency ranged between 24.3 and 46.7%, and were significantly higher than in healthy controls (2.4%, $P < 0.01$). In the same group, the frequency of HLA-B27 in young (≤40 years) and in male patients was significantly higher than in the old and in female (Table 2).

During a 1-year follow-up, 102 subjects were definitely diagnosed as AS, but only one HLA-B27-negative patients. HLA-B27-positive rate is 99% in definite AS patients. Of 102 definite patients, 79 were men and 23 women (M/F 3.4), with a mean age of 28.3 ± 9.9 (range 6–57). Sixty-nine (67.6%) definite patients were distributed in group 1 (low back pain and stiffness) and the higher incidence of AS in group 1 (28.5%) was also observed. In group 6 (alteration of skin), no one was confirmed as AS. The incidence of AS in the same group was found with a similar pattern to the frequency of HLA-B27, in male and young patients significantly greater, except group 4 (peripheral arthritis). Table 3 shows the distribution of definite AS patients and comparison of AS incidence in different groups.

Table 2 Comparison of the frequencies of HLA-B27 in patients suspected of AS with in healthy controls and comparison on the basis of sex and age in the same group

Group	HLA-B27 positive *n* (%)	Sex			Age		
		Male *n* (%)	Female *n* (%)	*P*	≤40 years *n* (%)	>40 years *n* (%)	*P*
Total number	366 (36.0)*	291 (52.0)	75 (16.4)	<0.01	302 (49.3)	64 (15.8)	<0.01
1. Low back pain and stiffness	113 (46.7)*	89 (70.6)	24 (20.7)	<0.01	94 (58.0)	19 (23.8)	<0.01
2. Alternating buttock pain	88 (33.5)*	65 (44.2)	23 (19.8)	<0.01	71 (42.0)	17 (18.0)	<0.01
3. Enthesitis	21 (26.6)*	19 (38.0)	2 (7.0)	<0.01	20 (45.5)	1 (2.9)	<0.01
4. Peripheral arthritis	111 (34.1)*	90 (52.0)	21 (13.7)	<0.01	87 (44.8)	24 (18.2)	<0.01
5. Ocular inflammation	24 (34.8)*	20 (46.5)	4 (15.4)	<0.01	23 (54.8)	1 (3.7)	<0.01
6. Alteration of skin	9 (24.3)*	8 (38.1)	1 (6.3)	<0.01	7 (31.8)	2 (13.3)	<0.01
Healthy controls	4 (2.4)	3 (3.1)	1 (1.4)		4 (3.5)	0 (0.0)	

* $P < 0.01$ compared with healthy controls

Table 3 Distribution of confirmed AS patients and comparison of AS incidence in different groups

Group	Confirmed AS patients *n* (%)	Sex			Age		
		Male *n* (%)	Female *n* (%)	*P*	≤40 years *n* (%)	>40 years *n* (%)	*P*
Total number	102 (10.0)	79 (14.1)	23 (5.0)	<0.01	82 (13.4)	20 (4.9)	<0.01
1. Low back pain and stiffness	69 (28.5)*	54 (42.9)	15 (12.9)	<0.01	58 (35.8)	11 (13.7)	<0.01
2. Alternating buttock pain	7 (2.7)	6 (4.0)	1 (0.8)	<0.01	6 (4.0)	1 (0.8)	<0.01
3. Enthesitis	10 (12.7)	8 (16.0)	2 (6.9)	<0.01	9 (20.4)	1 (2.9)	<0.01
4. Peripheral arthritis	7 (2.1)	4 (2.3)	3 (2.0)	>0.05	3 (1.5)	4 (3.0)	>0.05
5. Ocular inflammation	9 (13.0)	7 (16.3)	2 (7.7)	<0.01	7 (16.7)	2 (7.4)	<0.01
6. Alteration of skin	0						

* $P < 0.01$ compared with other patients groups

Discussion

Currently, there is a delay of 5–10 years between the onset of the first symptoms and diagnosis, which is unacceptably long [18]. The modified New York classification criteria are often used for diagnostic purposes. The concept of AS without sacroiliitis may seem absurd, because inflammation of the sacroiliac joints is the hallmark of the disease. Radiological changes occur slowly in AS [19]. Only about 30% of patients with early disease have radiographic changes in their sacroiliac joints at first presentation [20]. Computed tomography and dynamic magnetic resonance imaging may be easy to interpret evidence of sacroiliitis, but be high cost for patients in lower socioeconomic groups and not popular in a developing country like China. There is a need for new criteria for early diagnosis of AS [21]. Our studies confirmed that a relatively cheaper HLA-B27 test could be helpful to define a Chinese patient suspected of AS.

First, because this was the first study on the frequency of HLA-B27 in Chinese patients suspected of AS, an unexpected high frequency (36.0%) was found in 1,016 patients. In the groups studied, the frequency ranged between 24.3 and 46.7%, and were significantly higher than in healthy controls (2.4%, $P < 0.01$). It suggests there is a remarkable clinical significance of HLA-B27 typing in Chinese patients suspected of AS. In addition, despite the strong linkage of AS with HLA-B27, fewer than 5% of B27-positive individuals in the general population develop AS [6, 10, 22]. The B27 test cannot be thought as a routine test for screening AS in random population, which would merely enhance mental-economic burden of B27-positive subjects. Of course, it is unnecessary in definite AS, or in advanced AS, since HLA-B27 as the best genetic marker for the diagnosis of AS not as reliable indicators of disease activity or outcome [23, 24]. From our studies, the frequencies of HLA-B27 in healthy controls and in definite AS patients were 2.4 and 99.0%, respectively. This also implied that it was unnecessary for routine work to determine HLA-B27 in the general and definite AS population.

Secondly, the diagnostic value of a single parameter is determined by its specificity and sensitivity [26]. Although HLA-B27 typing in the diagnosis of AS is often questioned, HLA-B27 genotype is one of main laboratory parameters [25–28]. In our studies, the frequencies of

HLA-B27 in healthy controls (2.4%) were very close to 2.36% found by Ma et al. [29]. HLA-B27 was present in up to 99.0% in definite AS patients, which were compatible with previous reports that HLA-B27-positive rate in AS patients was more than 90% [30]. The specificity of HLA-B27 typing is determined by the frequency of HLA-B27 in the given population and the sensitivity is the percentage of HLA-B27 in AS patients [13]. Thus, the B27 test for AS has 97.6% specificity and 99.0% sensitivity in Chinese population. With its high specificity and sensitivity for AS, the B27 test is particularly useful in the diagnosis of AS.

It is noteworthy that 67.6% definite patients were distributed in group 1 (low back pain and stiffness for >3 months) with higher incidence of AS (28.5%). The results indicated that among B27(+) Chinese patient suspected of AS, the ones who presented low back pain and stiffness for >3 months were earlier to develop AS than others in a short time (1 year). In other words, a combination of the major manifestation (low back pain) with the important parameter HLA-B27 would be an aid to reach an early diagnosis with good certainly. It did confirm the findings of other reports that patients with chronic back pain for >3 months should be screened for the presence of inflammatory back pain, the presence of HLA-B27, or for evidence of sacroiliitis by any imaging method [9, 25, 31–34]. Meanwhile, some results were observed that the frequency of HLA-B27 and incidence of AS were strongly influenced by age- and sex-related factors and showed a young (≤40 years) and male preponderance. One related study concluded that androgenic steroids imbalance in preteen and younger adult ages may contribute to manifestations of AS by complex and currently unknown mechanisms [35].

On these grounds, it is necessary to determine HLA-B27 in Chinese patients with suspected of AS, particularly a young men (≤40 years) who presents with low back pain and stiffness for >3 months. HLA-B27 is one of sensitive diagnostic tools for early AS in Chinese population.

Finally, there are certain limitations in our study. First, lack of validated criteria for the diagnosis of early AS makes it difficult to choose patients objectively. Second, 1-year follow-up term is so short that there are limited results to be summarized. For example, the results in groups 4 and 6 (peripheral arthritis and alteration of skin) were different with others, might be caused by short-term follow-up. Moreover, it seemed to exhibit that, for Chinese patients suspected of AS, the ones presented alteration of skin would developed AS slowly or rarely and the male presented peripheral arthritis had no difference in the incidence of AS with the female within 1 year. These need to be further confirmed. Therefore, more long-term follow-up data and validated criteria for the diagnosis of early AS will be necessary.

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