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Association between HLA-B*27:04 and genetic susceptibility to ankylosing spondylitis in Hunan Province

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ABSTRACT

Objective: Human leukocyte antigen (HLA) B27 is a susceptibility allele of ankylosing spondylitis (AS), and HLA-B27 antigen typing is an important indicator for clinical diagnosis of AS, but current typing methods such as sequence specific primer polymerase chain reaction (PCR-SSP) still possess limitation. Therefore, this study aims to analyze the correlation between B27 subtypes and susceptibility to AS in Hunan Province by applying high-resolution polymerase chain reaction-sequence-based typing (PCR-SBT).

Methods: Peripheral blood of 116 patients with suspected AS (suspected AS group) and 121 healthy volunteers (control group) admitted to the Second Xiangya Hospital from January 2020 to December 2020 were collected for HLA-B genotyping by PCR-SBT. Among the patients in the suspected AS group, 23 patients were finally diagnosed with AS (confirmed AS group), and the remaining 93 undiagnosed patients served as the non-confirmed AS group. PCR-SBT and PCR-SSP were used to detect HLA-B27 typing in 116 patients with suspected AS, and the results of the 2 methods were compared.

Results: The HLA-B27 allele frequency in the suspected AS group was significantly higher than that in the control group [11.63% vs 2.48%; $P<0.001$, odds ratio (*OR*)=5.18, 95% confidence interval (*CI*) 2.097 to 12.795]. B*27:04, B*27:05, B*27:06, and B*27:07 were detected in the suspected AS group and the control group. The frequency of the B*27:04 allele in the suspected AS group was significantly higher than that in the control group (9.48% vs 1.24%; $P<0.001$, *OR*=8.346, 95% *CI* 2.463 to 28.282). The positive rate of B27 in the suspected AS group and the confirmed AS group (B27+/+ and B27+/−) was significantly higher than that in the control group ($\chi^2=16.579$, $P<0.001$; $\chi^2=94.582$, $P<0.001$, respectively). Among the confirmed AS group, 21 were HLA-B27 carriers, and the B27 positive rate in the confirmed AS group was 91.3%. PCR-SBT could achieve high resolution typing of the HLA-B gene locus, with higher sensitivity, specificity, positive

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predictive value, negative predictive value, and accuracy than PCR-SSP.

Conclusion: PCR-SBT typing analysis shows a strong correlation between HLA-B * 27:04 and AS in Hunan province. The PCR-SBT method can be used as the preferred option for the auxiliary diagnosis of clinical AS.

KEY WORDS ankylosing spondylitis; human leukocyte antigen-B*27:04; genetic susceptibility; polymerase chain reaction sequence-based typing

湖南地区携带HLA-B*27:04等位基因人群与强直性脊柱炎的易感性具有强相关性

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[摘 要] 目的：人类白细胞抗原(human leukocyte antigen，HLA)B27是强直性脊柱炎(ankylosing spondylitis，AS)的易感等位基因，HLA-B27抗原分型是临床诊断AS的重要指标，但目前的分型方法如序列特异引物聚合酶链反应技术(polymerase chain reaction-sequence specific primer，PCR-SSP)等仍存在一定的缺陷。因此，本研究旨在应用高分辨率聚合酶链反应直接测序分型法(polymerase chain reaction-sequence-based typing，PCR-SBT)分析B27亚型与湖南地区强直性脊柱炎易感性的相关性。**方法：**收集2020年1至12月在湘雅二医院门诊就医的116例疑似AS患者(疑似AS组)和121名健康志愿者(对照组)的外周血，采用PCR-SBT进行HLA-B基因分型。在疑似AS组患者中，23名患者最终被确诊为AS(AS确诊组)，其余的93名未能确诊的患者为非AS确诊组。采用PCR-SBT和PCR-SSP检测116例疑似AS患者的HLA-B27分型，并比较2种方法的检测结果。**结果：**疑似AS组HLA-B27等位基因频率显著高于对照组[11.63% vs 2.48%；P<0.001，优势比(odds ratio，OR)=5.18，95%置信区间(confidence interval，CI) 2.097~12.795]。疑似AS组和对照组均检出B*27:04、B*27:05、B*27:06、B*27:07。疑似AS组B*27:04等位基因频率明显高于对照组(9.48% vs 1.24%；P<0.001，OR=8.346，95% CI 2.463~28.282)。疑似AS组和AS确诊组B27阳性率(B27+/+和B27+/−)均显著高于对照组(分别χ^2=16.579，P<0.001；χ^2=94.582，P<0.001)。在AS确诊组中，21例为HLA-B27携带者，AS确诊组B27阳性率为91.3%。PCR-SBT方法可对HLA-B基因位点进行高分辨分型，其敏感度、特异度、阳性预测值、阴性预测值、准确度均高于PCR-SSP法。**结论：**应用PCR-SBT检测出HLA-B*27:04与湖南地区AS具有强相关性。PCR-SBT可作为临床AS辅助诊断的优选方案。

[关键词] 强直性脊柱炎；人类白细胞抗原-B*27:04；遗传易感性；聚合酶链反应直接测序分型法

Ankylosing spondylitis (AS) is one of the main forms of chronic inflammatory arthritis and is a typical representative of a group of chronic autoimmune joint diseases, spondyloarthropathy[1]. It is characterized by arthritis affecting the spine and pelvis. It specifically involves the sacroiliac joints and initially causes pain and reversible stiffness (morning stiffness that disappears with exercise later in the day); however, in some cases, it causes progressive joint fusion, irreversible stiffness, and deformity[2]. Because of the insidious and progressive nature of AS, the time delay from symptom onset to diagnosis can be as long as 8−10 years[3], hence early diagnosis of AS is particularly important.

Study[4] has confirmed that susceptibility to AS is genetically determined, with a genome-wide association analysis identifying 113 alleles associated with AS. Among these, AS has a strong association with the HLA class I molecule HLA-B27. Approximately 85%－95% of AS patients in the United States, Europe, and China are HLA-B27-positive[5]. A case-control study showed that HLA-B27-positive AS patients had a significantly

higher incidence of disease before age of 40 than HLA-B27-negative AS patients[3, 6]. AS is difficult to diagnose because its symptoms are similar to many diseases; therefore, the detection of HLA-B27 is of great significance in the early diagnosis of AS.

The frequency distribution of HLA-B27 subtypes varies in different racial and ethnic populations worldwide. And the strength of association between HLA-B27 subtypes with AS varies, too. For example, HLA-B*27: 02, B*27: 04, and B*27: 05 are positively correlated with AS, whereas B*27: 06 and B*27: 09 are negatively correlated with AS[7]. HLA-B*27: 02 and HLA-B*27: 05 are the predominant subtypes in Caucasian populations, and HLA-B*27: 02 is more common in Middle Eastern (Ashkenazi) and North African (Arab/Berber) populations[8]. HLA-B*27: 04 is the main HLA-B subtype in the Chinese population[9].

The detection methods for B27 in clinical settings primarily include microcytotoxicity test, real-time quantitative polymerase chain reaction (PCR), flow cytometry, and PCR-sequence specific primer (PCR-SSP), however, the high-resolution PCR-sequence-based typing (PCR-SBT) has not yet been established. In this study, we used PCR-SBT to genotype the HLA-B27 subtypes of suspected AS patients and healthy controls in clinical outpatient clinics in Hunan Province, and compared the results with the final confirmed AS cases. Additionally, a comparison between PCR-SBT and PCR-SSP methods was conducted.

1 Subjects and methods

1.1 Patients and controls

A total of 116 consecutive patients with suspected AS due to neck, waist, back, sacroiliac joint pain, or eye lesions at the Second Xiangya Hospital of Central South University from January 2020 to December 2020 were included as research subjects (suspected AS group), including 89 males and 27 females, with an average age of (34±16) years. To facilitate the analysis and comparison, 121 healthy people who underwent physical examination in the Physical Examination Center of the same hospital during the same period were included in this study (Control group). The group consisted of 74 males and 47 females with an average age of (45±19) years. Statistical analysis indicated no significant differences in gender or age between the 2 groups (both $P>0.05$).

The New York criteria for AS[10] revised by the American Rheumatology Association (ARA) was used as AS diagnostic criteria. Clinical criteria: 1)Low back pain for more than 3 months which improves with exercise, but is not relieved by rest; 2)limitation of lumbar flexion, lateral flexion, and extension activities; 3)limitation of chest expansion relative to normal values corrected for age and sex. Radiological criteria: Unilateral sacroiliac arthritis grade 3－4 or bilateral sacroiliac arthritis grade 2－4. The diagnosis of AS was confirmed by meeting any of the radiologic and one or more clinical criteria. Twenty-three patients in the 116 suspected AS patients were diagnosed as AS (confirmed AS group), and other 93 suspected AS patients were named as a non-confirmed AS group. Exclusion criteria included patients with other autoimmune diseases, combined infectious diseases, malignant tumors, and other wasting diseases, and pregnant and lactating women. Informed consent was obtained from all patients and healthy controls.

1.2 HLA-B genotyping

PCR-SBT was used for HLA-B genotyping. First, genomic DNA was extracted from peripheral blood cells of patients in the suspected AS group and the control group, and the HLAssure SE B locus SBT kit (TBG Diagnostics Limited, USA; Cat. 50210) for HLA-B locus typing and sequencing of exons 2 and 3 of HLA-B. DNA sequencing was performed using an Applied Biosystems 3730 DNA analyzer. The samples were genotyped using AccuType™ software.

1.3 PCR-SSP

PCR-SSP is a commonly used method for detecting HLA-B27 typing. We utilized both PCR-SBT and PCR SSP methods to detect HLA-B27 typing in 116 patients with suspected AS. Subsequently, we compared their respective detection rates. Peripheral blood DNA extraction was performed using PCR-SSP detection kit (Search Biotech Co., Ltd, Nanjing, China). The procedures were performed strictly according to the instructions, and the Applied Biosystems 7000 PCR instrument was used for detection.

1.4 Statistical analysis

All statistical analyses were performed using SPSS software (Version 26.0). Categorical variables were presented as counts (*n*) and percentages (%). Chi-squared test were used for comparison between groups. Gene frequencies were determined according to the Hardy-Weinberg law. $P<0.05$ was considered statistically significant.

2 Results

2.1 HLA-B27 is strongly associated with AS

HLA-B genotyping was performed on DNA samples from the 2 groups, and the high-resolution typing results for HLA-B loci were transformed into corresponding antigenic typing designations. A total of 23 HLA-B alleles were detected (Table 1). The allele frequencies of B40 were the highest in the 2 groups (22.85% and 18.60%, respectively). Among them, 27 cases of B27 were detected in the suspected AS group and 6 cases in the control group, and the allele frequency in the suspected AS group was significantly higher than that in the control group (11.63% vs 2.48%, *OR*=5.18, 95% *CI* 2.097 to 12.795, $P<0.001$). The frequencies of other antigens were not significantly different between the 2 groups (all $P>0.05$). The results showed that HLA-B27 expression was strongly correlated with AS.

Table 1 Frequencies of HLA-B allele in the suspected AS group and the control group

Antigen	Suspected AS (2*n*=232)		Control (2*n*=242)		*OR*(95% *CI*)	χ^2	*P*
	No.	Proportion/%	No.	Proportion/%			
B7	2	0.86	4	1.65	0.517(0.094−2.852)	0.593	0.441
B8	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976
B13	18	7.75	23	9.50	0.801(0.420−1.526)	0.457	0.499
B62	32	13.79	35	14.46	0.946(0.564−1.587)	0.044	0.834
B27	27	11.63	6	2.48	5.180(2.097−12.795)	15.339	<0.001
B32	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976
B35	3	1.29	8	3.31	0.383(0.100−1.462)	2.117	0.146
B37	2	0.86	2	0.83	1.043(0.146−7.470)	0.002	0.966
B38	1	0.43	7	2.89	0.145(0.018−1.191)	4.325	0.038
B39	3	1.29	8	3.31	0.383(0.100−1.462)	2.117	0.146
B40	53	22.85	45	18.60	1.296(0.830−2.025)	1.304	0.253
B41	2	0.86	1	0.41	2.096(0.189−23.269)	0.379	0.538
B44	4	1.72	4	1.65	1.044(0.258−4.422)	0.004	0.952
B46	34	14.66	30	12.40	1.213(0.716−2.057)	0.517	0.472
B48	2	0.86	4	1.65	0.517(0.094−2.852)	0.593	0.441
B51	12	5.17	17	7.02	0.722(0.337−1.547)	0.708	0.271
B52	4	1.72	5	2.07	0.832(0.221−3.136)	0.074	0.707
B54	5	2.16	8	3.31	0.644(0.208−1.999)	0.588	0.443
B55	11	4.74	8	3.31	1.456(0.575−3.687)	0.634	0.426
B56	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976
B57	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976
B58	10	4.31	21	8.68	0.474(0.218−1.030)	3.696	0.055
B67	3	1.29	2	0.83	1.572(0.260−9.495)	0.247	0.619

HLA: Human leukocyte antigen; AS: Ankylosing spondylitis; *OR:* Odds ratio; *CI:* Confidence interval.

2.2 HLA-B27 allele is associated with AS

One case of B27+/+ was detected in the suspected AS group, with a frequency of 0.8% (1/116), which was also in the confirmed AS group, whereas no B27+/+ was

found in the control group. The frequency of patients with suspected AS carrying one B27 genotype (B27+/−) was 22.4% (26/116). The B27 positive rate (B27+/+ and B27+/−) was significantly higher in the suspected AS group than that in the control group (χ^2=16.579, P< 0.001). Twenty-one of 23 confirmed AS patients were HLA-B27 carriers, and B27 positive rate in the confirmed AS group was significantly higher than that in the control group (χ^2=94.582, P<0.001; Table 2), suggesting that carrying the HLA-B27 allele is associated with AS.

2.3 HLA-B*27: 04 is the allele for the strong association with AS

The allele frequencies of HLA-B subtypes were analyzed (Table 3). The B40 subtype, especially B*40:01, was the most common subtype in the suspected AS group and the control group, with 44 and 39 cases detected, and the allele frequencies were 18.97% and 16.12%, respectively. The second subtype was B*46:01, which was detected in 34 (14.66%) cases and 30 (12.40%) cases in the suspected AS group and the control group, respectively. Four HLA-B27 subtypes (B*27:04, B*27:05, B*27:06, and B*27:07) were found in the suspected AS group (Table 3), with allele frequencies of 9.48%, 1.29%, 0.43%, and 0.43%, respectively. Among them, the B*27:04 allele frequency of the suspected AS group was significantly higher than that of the control group (9.48% vs 1.24%; P<0.001, OR=8.346, 95% CI 2.463 to 28.282). However, there were no significant differences in the allele frequencies of B*27:05, B*27:06, and B*27:07 between the 2 groups (all P>0.05).

Table 2 Frequencies of HLA-B27 genotypes

Groups	n	B27+/+/[No.(%)]	B27+/−/[No.(%)]	B27−/−/[No.(%)]
Control	121	0(0)	6(4.96)	115(95.04)
Suspected AS	116	1(0.80)	26(22.40)	89(76.80)
Confirmed AS	23	1(4.35)	20(86.95)	2(8.70)

χ^2 tests were performed between the control group and the suspected AS group (χ^2=16.579, P<0.001), and the control group and the confirmed AS group (χ^2=94.582, P<0.001). HLA: Human leukocyte antigen; AS: Ankylosing spondylitis.

Table 3 Frequencies of HLA-B allele in the suspected AS group and the control goup

Allele	Suspected AS (2n=232)		Control (2n=242)		OR(95% CI)	χ^2	P
	No.	Proportion/%	No.	Proportion/%			
B*07:02	1	0.43	3	1.24	0.345(0.036−3.339)	0.926	0.336
B*07:05	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976
B*08:01	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976
B*13:01	14	6.03	13	5.37	1.131(0.520−2.461)	0.097	0.756
B*13:02	3	1.29	10	4.13	0.304(0.083−1.119)	3.579	0.059
B*13:21	1	0.43	0	0			
B*15:01	10	4.31	12	4.96	0.863(0.336−2.039)	0.112	0.737
B*15:02	16	6.90	10	4.13	1.719(0.763−3.869)	1.746	0.186
B*15:07	1	0.43	4	1.65	0.258(0.029−2.322)	1.694	0.193
B*15:12	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976
B*15:25	3	1.29	3	1.24	1.044(0.209−5.224)	0.003	0.959
B*15:27	1	0.43	5	2.07	0.205(0.024−1.770)	2.534	0.111
B*27:04	22	9.48	3	1.24	8.346(2.463−28.282)	16.109	<0.001
B*27:05	3	1.29	1	0.41	3.129(0.328−29.869)	1.096	0.295
B*27:06	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976
B*27:07	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976
B*32:02	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976

Table 3 (continued)

Allele	Suspected AS (2*n*=232)		Control (2*n*=242)		*OR*(95% *CI*)	χ^2	*P*
	No.	Proportion/%	No.	Proportion/%			
B*35:01	2	0.86	7	2.89	0.292(0.060−1.420)	2.622	0.105
B*35:05	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976
B*37:01	2	0.86	2	0.83	1.043(0.146−7.470)	0.002	0.966
B*38:02	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976
B*38:02	0	0	6	2.48			
B*39:01	3	1.29	6	2.48	0.515(0.127−2.085)	0.895	0.344
B*39:05	0	0	1	0.41			
B*39:09	0	0	1	0.41			
B*40:01	44	18.97	39	16.12	1.218(0.758−1.958)	0.666	0.414
B*40:02	6	2.59	1	0.41	6.398(0.764−53.559)	3.844	0.050
B*40:06	3	1.29	4	1.65	0.779(0.173−3.521)	0.105	0.745
B*40:48	0	0	1	0.41			
B*41:01	2	0.86	1	0.41	2.096(0.189−23.269)	0.379	0.538
B*44:03	4	1.72	2	0.83	2.105(0.382−11.605)	0.764	0.382
B*44:03	0	0	2	0.83			
B*46:01	34	14.66	30	12.40	1.213(0.716−2.057)	0.517	0.472
B*48:01	1	0.43	3	1.24	0.345(0.036−3.339)	0.926	0.336
B*48:03	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976
B*51:01	10	4.31	13	5.37	0.076(0.010−0.588)	0.289	0.591
B*51:02	2	0.86	4	1.65	0.517(0.094−2.852)	0.593	0.441
B*52:01	4	1.72	4	1.65	1.044(0.258−4.224)	0.004	0.952
B*52:04	0	0	1	0.41			
B*54:01	5	2.16	8	3.31	0.644(0.208−1.999)	0.588	0.443
B*55:02	11	4.74	8	3.31	1.456(0.575−3.687)	0.634	0.426
B*56:01	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976
B*57:01	1	0.43	1	0.41	1.043(0.065−16.778)	0.001	0.976
B*58:01	10	4.31	21	8.68	0.474(0.218−1.030)	3.696	0.055
B*67:01	3	1.29	2	0.83	1.572(0.260−9.495)	0.247	0.619

HLA: Human leukocyte antigen; AS: Ankylosing spondylitis; *OR:* Odds ratio; *CI:* Confidence interval.

2.4 PCR-SBT method has advantages in clinically assisted diagnosis

The respective detection rate of PCR-SBT and PCR-SSP were list in Table 4. The results showed that the PCR-SBT method demonstrated higher sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in comparison with the PCR-SSP method (Table 5).

Table 4 Results of HLA-B27 detected by PCR-SBT and PCR-SSP

Groups	PCR-SBT		PCR-SSP	
	Positive/No.	Negative/No.	Positive/No.	Negative/No.
Confirmed AS	21	2	20	3
Non-confirmed AS	6	87	8	85

HLA: Human leukocyte antigen; AS: Ankylosing spondylitis; PCR-SBT: PCR-sequence-based typing; PCR-SSP: PCR-sequence specific primer.

Table 5 Comparison of detection results by PCR-SBT and PCR-SSP

Methods	Sensitivity/%	Specificity/%	Positive predictive value/%	Negative predictive value/%	Accuracy rating/%
PCR-SBT	91.3	93.5	77.8	97.8	93.1
PCR-SSP	86.9	91.4	71.4	96.6	90.5

PCR-SBT: PCR-sequence-based typing; PCR-SSP: PCR-Sequence specific primer.

3 Discussion

AS is strongly associated with HLA-B27; however, different B27 alleles have different strengths of association with AS, making genetic testing more useful than serological testing. At present, the common methods of HLA DNA typing mainly include PCR-SSP, polymerase chain reaction-sequence specific oligonucleotide (PCR-SSO), and flow cytometry; however, these methods still have certain shortcomings, such as the possibility of misjudging some loci, and techniques yield low-resolution results. Compared with other genotyping methods, PCR-SBT has the advantages of good repeatability, high resolution, the ability to distinguish heterozygotes, and can be subject to a high degree of automation. It is currently the most accurate method for confirming HLA genotypes. In this study, we used PCR-SBT to genotype HLA-B27 subtypes in clinical outpatients suspected of having AS in Hunan, China, to explore the application of PCR-SBT-based detection of HLA-B27 in the clinical diagnosis of AS.

Our results showed that the frequency of the HLA-B27 allele in patients with suspected AS (11.63%) was significantly higher than that in healthy controls (2.48%), indicating that HLA-B27 is associated with AS. In the HLA-B27 subtype, the frequency of the B*27:04 allele was significantly higher in the suspected AS group (9.48%) than that in the control group (1.24%), indicating that HLA-B*27: 04 is the main subtype in suspected AS patients and carriers. This result is consistent with the results reported in Zhejiang Han Nationality[11], Beijing[12], Shanghai[13], and Jiangsu Province[13].

Study[14] indicates that the positive rate of HLA-B27 in patients with AS can reach 90%, whereas this is < 8% in healthy controls. Our study showed that the B27+/+ genotype was present only in confirmed and suspected AS cases, whereas B27+/+ was absent in healthy controls. The positive rate of B27 in the suspected AS group and the confirmed AS group (B27+/+ and B27+/−) was significantly higher than that in the control group (χ^2=16.579, P<0.001; χ^2=94.582, P< 0.001, respectively), suggesting that carrying the HLA-B27 allele is associated with AS.

There are differences in HLA-B27 subtypes in different regions and ethnic groups. In this study, B*27:05 was the second-most common HLA-B27 allele in patients with suspected AS, and its frequency was higher than that of controls, but the difference was not statistically significant. This result is consistent with the results of study[11] on HLA-B27 in the Chinese Han population and a meta-analysis[15]. In addition, the allele frequencies of B*27:06 and B*27:07 were low in Hunan Province, but the prevalence of B*27:06 was relatively high in Thailand, Indonesia, and Malaysia [16]. It is worth noting that the B*27:15 subtype is considered a susceptibility gene in AS patients in Lishui, Zhejiang[11], whereas B*27:15 was not detected in Hunan Province, indicating the regional diversity of HLA-B27 subtypes.

We used PCR-SBT and PCR-SSP to detect HLA-B27 in 116 patients with suspected AS to compare the 2 mothods in the diagnosis of AS. The results showed that the PCR-SBT had higher sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in comparison with PCR-SSP. PCR-SBT has certain advantages in the diagnosis of AS.

In conclusion, the PCR-SBT typing method was effectively used to type HLA-B27 in suspected AS patients in Hunan Province, which was shown a strong correlation with AS. Its main subtype is HLA-B*27:04 with PCR-SBT typing method, and the positive rate of HLA-B27 in suspected AS patients is significantly higher than that in healthy people. Carrying the HLA-B27:04 allele is strong associated with AS. This study preliminarily reflectes that AS patients in the Hunan Province have a strong correlation with HLA-B27*04 allele, and the PCR-SBT typing method may provide a more accurate reference value for the early assisted diagnosis of AS in the region. PCR-SBT is of great significance for the early auxiliary diagnosis of AS.

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