

CLINICAL STUDY

HLA-B27 subtypes in patients with spondylarthropathies, IgE levels against some allergens and their relationship to the disease parameters

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Abstract: In suitable genetic backgrounds, some exogenous and/or endogenous antigens may cause SpA. In this study, we investigated HLA B27 subtypes and its relationship to some allergens and clinical findings in a group of SpA patients.

Forty-eight patients (19F, 29M) with SpA (27 with ankylosing spondylitis, 5 with reactive arthritis, 15 undifferentiated and 1 with psoriatic arthritis) were included to the study. HLA-B alleles have been assessed using the LiPA (Line Probe Assay) reverse hybridization principle method. The allergens studied were following: egg white, yolk, wheat flour, hot pepper, tomatoes, olive, onion, chicken, black tea, sheep cheese, penicillin panel (m1, m25, m28, m30), fungus panel (m1, m2, m3, m6), and housemix panel (e1, e2, d1, d2, m2, m3). 59.3 % of the patients were positive for HLA-B27. Of these patients, 53.6 % had B*2702 allele which was the most common, followed by B*2708 (21.1 %) and B*2701 (10.5 %). HLA-B27 was positive in 70 % of the ankylosing spondylitis patients and 52 % had B*2702 subgroup and B35 was the most common subgroup among the patients who were HLA-B27 negative.

Allergic reactions against these 13 allergens were more severe in patients HLA-B27 positive. The most frequent allergic reactions were against the onion and housemix panel, followed by red pepper, tomatoes, sheep cheese and olive. HLA-B*2702 and HLA-B*2701 subgroups had more severe allergic reactions that correlated with a disease severity ($p < 0.001$).

These results indicate that B*2702 and B*2708 is more frequent in our region in contrast to B*2705 which is more commonly found all around the world and that our region represents a heterogeneous distribution. IgE levels against some allergen were found higher in patients with SpA (Fig. 2, Tab. 5, Ref. 37). Full Text (Free, PDF) www.bmj.sk.

Key words: spondyloarthropathy, ankylosing spondylitis, HLA-B27, subtype, allergy.

There is much evidence showing that HLA-B27 has a direct role in ankylosing spondylitis (AS) and its related spondylarthropathy (SpA) group of diseases although its molecular base is not sufficiently understood. There are various allergic elements in the environmental (1, 2).

27 sub-groups of HLA-B27 which codes 24 different proteins have been defined. B*2705, B*2702 and B*2704 are the one, which are determined in epidemiologic studies as having certain relations with patients with SpA. Any relationship between B*2706 and disease could not be found in Indonesia, Taiwan and Singapore. B*2709, that has only one main difference from B*2705, is found as having no relation with SpA among the Italians in the Sardinia Island (3). These differences must have an important role in the pathogenesis.

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In this study; the sub-groups in HLA-B27 positive patients in a SpA patient group in the region, the genotypes in HLA-B27 negative patients, the specific IgE antibody level of the patients against a group of antigenic agents and their relations were studied.

Materials and method

Study Group

Seventy one spondylarthropathy patients (46 men and 25 female), who were suitable for ESSG diagnosis criteria, were included at the beginning of the study.

The patients, who had an active infection or had another active illness in the last month or had an active hepatitis and clearly allergic reactions, were not included in the study. As a result, a study group consisting of 48 patients (19 F/29 M) was formed.

The demographical questionnaires, physical examinations, anthropometric measures, BASFI, BASDAI, HAQ-S and NHP (Nottingham Health Profile), evaluations of the patients were performed by the same investigators (4, 5).

Tab. 1. Allergen panel in this study.

Allergen
Egg white
Yolk
Wheat flour
Hot pepper (red pepper)
Tomatoes
Olive
Onion
Chicken
Black tea
Sheep cheese
Penicillin panel (m1, m25, m28, m30)
Fungus panel (m1, m2, m3, m6)
House mix panel (e1, e2, d1, d2, m2, m3)

Tab. 2. Demographic data in study groups.

	Patients group (71)	Study group (48)
Age (year)	36±10	36.06±10
BMI (kg/m ²)	23.16±3.03	23.83±3.9
Disease duration (year)	10.11±8.6	10.24±9
Sex F/M	25/46	19/29

Laboratory Measures

The blood samples were collected from the cubital vein at 09:00–11:00 in the morning. All samples except the allergic antibodies and HLA-B allele analysis were studied on the same day with the laboratory methods applied routinely. The blood that was collected to study the specific IgE allergic antibodies was processed by centrifuge and the serum was separated. The blood samples which were taken into EDTA tubes for the analysis of HLA-B alleles were collected and sent to the laboratory in order to perform an analysis for the DNA isolation required in four days. During this period, the tubes were kept at +2 and +8 temperatures.

HLA-B alleles analysis

The HLA-B subtyping has been studied by the PCR hybridization with the LiPA (Line Probe Assay) reverse hybridization principle method. The determination of HLA-B alleles was hybridized with the two typing strips (1999 version) on which 60 special DNA probe lines and 2 control lines are fixed on the Amplification products (6).

Analysis of the allergy panel

The serum samples were preserved at -18 degree until the study was performed and then they were studied in our Immunology laboratory using the Dr. Fooke EAST (specific IgE Enzyme-Allergo-Sorbent-test) kit and the specific IgE level TECAN device (F-039100, Austria) against the allergens shown in Table 1 (7).

Statistics

The findings were arranged by the SPSS 10.0 packet statistics program in the Windows environment. In addition to the

Tab. 3. The spondylarthropathy type.

Distribution in the study group	n (%)
AS	27 (56.3)
ReA	5 (10.4)
Undifferentiated SpA	15 (31.3)
PsA	1 (2.1)
Total	48

descriptive statistical methods, the chi-square test and Fischer's Exact test were performed and Pearson correlation coefficient was calculated. The values $p < 0.05$ in the assessments were accepted as meaningful from the statistical point of view.

Results

All HLA-B allele types and 13 group allergy panels planned for 48 patients included in the study were completed. The demographical characteristics of the patients and study group are given in Table 2.

HLA-B27 antigen was found positive in 64% of patients. HLA-B27 was found positive in 28 patients (58.3 %) in the group where HLA alleles were studied. The rheumatoid factor was found negative in 46 of 48 patients (95.8 %). It was also determined that 5 patients had uveitis, 9 patients have never used medicine and the others have used one or two DMARD and various NSAIDs.

The spondylarthropathy type distribution in the study group is shown in Table 3 and the distribution of the SpA subtypes according to alleles was shown in Table 4. It was determined that 66.7 % of HLA-B*2702 subtype in SpA had AS.

When the study group was taken into consideration, it was observed that B*2702 allele was found frequently (31.3 %) but when the HLA-B27 positive patients are taken into account, the B 2702 rate was found in 53.6 % and B 2708 was found in 21.1 % and B 2701 was found as the third (10.5 %) in frequency. Also we found that the clinical status of the patients with B*2708 subtype was better and was more severe in patients having B*41 and 08 with the 2702 group and was seen together with B*1301 in patients in the 2701 group and it was mostly seen with peripheral joint involvement and enthesitis.

We observed that some patients were included in the 03, 09, 05, 13 subtypes due to weak reaction but this was also seen only in few patients. And we found that there was no significant differences between the B27 negative and positive patients but that it was more severe in B*2701 patients when the severity of disease are classified as light, average and high by taking into account BASDAI, BASFI ve HAQ-S (Tab. 5).

It was observed that the subtype distribution in HLA-B27 negative patients was equal according to gender but in HLA-B27 positives patients there were more male patients in the B*2702 subtype (Fig. 1).

In summary; the most observed subtypes in our study group were B*2702 and 2708. Together, mostly 2702 and B*1, B*4

Tab. 4. The distribution of the SpA subtypes according to alleles.

	2702	2708	2710	2701	HLA-B 27-	27g	Total
AS	10	4	1	2	8	2	27 (% 56.13)
ReA	1		1		3		5 (% 10.4)
Undifferentiated SpA	4	2		1	8		15 (% 31.3)
PsA					1		1
	15	6	2	3	20	2	48

*HLA B27g : 2703 / 09 / 13 / 052

and B*5 and 2708 were present. 2 of the HLA-B27 negative patients were in the 08 subtype, two patients were in the B*39 subtype and six patients were in the B35 subtype.

Allergy panel results of the study group

It was observed that specific IgE level in HLA-B27 positive patients were higher than in negative patients. The most significant reaction was against the onion and housemix panels (Fig. 2). Red pepper, tomato, sheep milk and cheese and olive were the other significant allergens. It was also observed that the IgE level against the sheep cheese, between HLA-B27 positive and negative individuals was little different. We observed that in patients with B2702 and B*2701 subtypes, the allergic reaction levels were higher than in other subtypes. And we found that the severity of allergic reactions was positively related to the severity of the disease ($p < 0.001$).

In summary, we observed that there was an allergic background in the study group and that this allergic background was more significant especially in the HLA-B27 positive individuals and the reactions against onion, housemix and fungus panels were more severe.

Discussion

The spondylarthropathy group diseases are in a strong relation to HLA-B27 (8, 9). This strong relation shows differences not only in the SpA group disease varieties but also in various races and ethnic groups. There are also regional and geographical differences.

The HLA-B27 subtypes differ from each other with one or more amino acid (10). The HLA-B*2705 is the commonly reported subtype in many study groups and it has a clear relation to AS and also the SpA group and it is mostly seen in the Northern Europe (90 %), west Siberia and North America Indians (99 %), (10–12). B*2704 is mostly seen after B*2705 in Asia (11, 12).

The HLA-B*2701 is a rare subtype and it is reported at least in one individual in caucasian, Asia, Mixed Race and African Americans (12). We determined B*2701 subtype (10.5 %) in three patients, two were brothers. The clinical status of the two brothers was severe peripheral arthritis and enthesitis compared to the other spondylarthropathy patients. AS was obvious in both. The concomitant presence of B*2701 and B*1302 in these three

Tab. 5. Severity of disease and HLA subtypes.

	Severity of disease			Total
	mild	moderate	severe	
HLAB27-	10	5	5	20
2702	8	2	5	15
2708	3	2	1	6
2710	2			2
2701	1		2	3
27g			2	2
HLAB27+	14	4	10	28

patients was also interesting. It was reported that B13 was seen in some dermatological diseases, especially in a family having familial discoid LE (14), in children with chronic nephrotic syndrome (15) and in patients with psoriasis (16, 17).

It was reported that HLA-B*2702 was seen between 4–10 % in B-27 positive individuals in the Northern Europe, 20 % in the Iberian Peninsula (Spain and Portugal) and 55 % in Semitic populations (10, 18, 19). This type is seen together with SpA. In other study of 38 HLA-B27 positive patients with AS it was reported as B*2702; 26.3 %, B*2705; 71.1 %, B*2708; 2.6 % in Samsun, Turkey (20). B*2702 rate was 53.6 % in our SpA patients with HLA-B27 positive and 47 % in our patients with AS. This situation can be interpreted as the regional differences.

HLA-B*2704 was also reported as the most frequent SpA related subtype among the Japanese and Chinese in Asia (10). B*2706 and B*2704 was reported in equal frequency and had poor relation to SpA in Thailand. These sub-groups were not observed in our study group as stated above.

The relation of HLA-B*2707 to the disease can be rare in Europe and India but B*2704 and B*2705 are seen frequently (11, 12). It was reported that HLA-B*2705 is the frequently seen subtype in Korean SpA patients and healthy individuals (21, 22). In a study among Danish AS patients and healthy individuals, it was reported that the rates of HLA-B*2705 was 90.2 % and HLA-B*2702 was 9.8 % in healthy individuals and there was only HLA-B*2705 in AS patients (13). B*2705 and B*2704 were not observed in our study group except in 2 patients who had poor reaction. However, other subtypes may be observed even if they are less frequent. And this situation shows that our region is more different than the others.

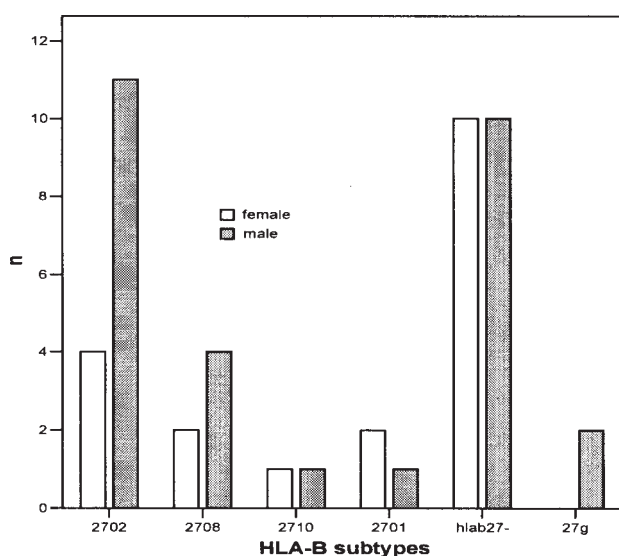


Fig. 1. According to gender, HLA-B27 subtypes in study group.

HLA-B*2708 is a rare subtype in Europe and it has a relation to AS in some families. Five different subtypes B*2705, B*2702, B*2703, B*2707 and B*2708 were found in a large family in the Azores Island, Portugal. In our study group, B*2708 was found in HLA-B27 positive patients at the rate of 21.4 % and two-third of this was AS. This shows that B*2708 subtype is the second most frequent sub-group in our region.

In literature it was reported that HLA-B*2709 was seen unrelated to AS especially in Sardinia people (11, 18, 23). HLA-B*2710 is a rarely seen subtype and it was reported in a white American family with SpA. B*2710 was determined in a patient with AS and a patient with RA in our study group and it was also observed that the course of the diseases were good.

The most frequent allele in HLA-B27 negative patients in our study group was determined as B*35 (45 %). It was mentioned in a study that there was a relation between hand OA and B*35 allele (24). It was reported that B*51 was much more and B*35 less frequent in Behcet disease with thrombophlebitis, (25) and it was reported in another study that B*35 was seen more in patients with pemphigus (26). This shows that the allele is a genetic determinant that should be taken into account as much as HLA-B*27.

It is known, that HLA-B51 is an important genetic determinant with a relation to the Behcet disease. There was a linkage disequilibrium between HLA-B51 and B*2702 among our patients compared to other patients. This situation is very interesting because this subtype was more frequently than B*5112. It was also reported that there was a stronger relation between B*5101 and 08 and the Behcet disease (27).

The rheumatic diseases are not diseases, which can be seen as groups in certain time and place. It is a commonly thought that the environmental factors often initiate the autoimmune response (28, 29). In our opinions, the allergic reactions are the situations to be examined in autoimmune diseases.

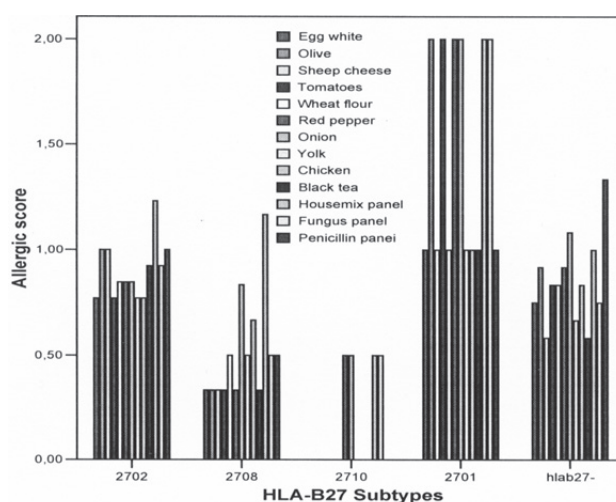


Fig. 2. According to HLA-B27 subtypes, allergen panel in study group.

It was observed in our study that IgE level of HLA-B27 positive patients against the allergens studied were a little higher. There was also a high reaction against the onion and housemix panels. 32.5 % of the patients have shown a high reaction and 20 % of the patients have shown a doubtful reaction. This reaction was found much more frequently in HLA-B*2702 and HLA-B*2701 patients.

It was reported that rheumatic symptoms started in people who work in moist environment and houses made of soil and actinobacteria and insineration were seen in those environments (28). The joint symptoms in 11 of 16 workers started when they began to work in these moist environments and, AS and than psoriatic arthritis were diagnosed in one of these workers and almost all of them had joint symptoms.

In another study, it was reported that the inflammatory rheumatic diseases (4 ReA, 4 AS and 2 SS) developed in 10 people among the workers who work in a place where there was moist and contamination and ventilation problem (29). The authors have interpreted this situation as some trigger factors available in moist environments.

Onion is a food type that may cause allergic reactions (urticaria, anaphylaxis). It contains little water, volatile oil and high amount of sulphate. The allergen, which may also be found in nut extract, was defined in onion (30). The onion is the allergen, to which our patients showed the most severe reaction and this situation shows that the onion should be analyzed in details.

Sheep milk and sheep cheese is the food types which are mostly consumed in our country and they showed higher IgE level in patients, especially in those whose diseases were more severe. It was reported that some food such as fish, egg and cheese may cause attacks in palindromic rheumatism (31). The cheese contains thyramine and histamine and its most allergic content was reported as casein (30).

Olive is a food that is consumed especially in the Mediterranean and its surroundings and the fruit and oil have an important role in kitchens. It is known that olive pollens are so allergic that hay fever is frequently seen in places where olive is consumed.

It was reported that it affected the Th2 response in mice that were sensitized with olive pollens (32). Also, the high IgE level against the antigen specific to olive was observed in our patients with more severe and active diseases.

Tomato is a food rich in vitamins A and C, calcium and potassium. In half of the oral allergic patients there were 4 proteins related to IgE (33). It was also mentioned that there was a common allergen called papathine found in tomato, potato and latex (34). It was reported that the lycopene in tomato has a preventive role in prostate cancer (35). It was also mentioned in a study that the food diets including little carotenoid can decrease IL-2 and IL-4 secretions and tomato juice addition can improve this. It was stated that there was a meaningful improvement in IL-2 (36). This may be interpreted that tomato can affect the Th1 response. From this point of view, it should be studied in rheumatic diseases.

A house dust may contain more than one mite that can be seen all over the world. *D. pteronyssinus* (d1), *Dermatophagoides farinae* (d2) and *D. microceras* (d3) can be seen everywhere but there may be some geographical differences. It was reported that the most commonly seen type is the *Dermatophagoides farinae* on the furnishings such as bed, pillow and furniture in locations, where the moist rate is above 45 % and the altitude is low (37).

It is clearly seen in B*2701 and 2702 sub-groups that the reaction against the house panel was high in our study group, therefore, the genetic background of the disease may affect the response to the allergens and there may be an affect on the progress or etiopathogenesis. There may be also a relation to the severity of the disease at least in HLA-B27 positive individuals.

In summary, HLA-B27 and its subtypes in our study group consisted of patients with spondyloarthropathy. The reaction levels of the patients against the allergens comprising of 13 groups were studied. B*2702 and secondly B*2708 was determined frequently in HLA-B27 positive patients. This rate was similar to patients with AS. B*2701 sub-group was observed rarely but the the disease was more severe. Regarding the distribution according to the gender, it was observed more in men in the B*2702 group and an equal distribution was observed in the HLA-B27 negative patients.

It was also found that the allergic reactions were severe in the HLA-B27 positive and B*2702 sub-group and the allergic reaction against the onion and house mix panels were clearer.

In our region, these results showed that B*2702 and B*2708 subtype were more frequent than B*2705, which is common in majority of the world. Additionally, it is also thought that some allergens may have an important role in the etiopathogenesis of SpA. An original study may be conducted on this aspect. Our study may be accepted as the first study from this point of view.

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