# Familial Aggregation of Ankylosing Spondylitis in Southern China

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***ABSTRACT.*** ***Objective.*** To study the familial aggregation of ankylosing spondylitis (AS) in southern China and to compare the clinical and laboratory characteristics between the probands and their first-degree relatives with AS.

***Methods.*** On the basis of questionnaires to 473 patients with AS, 402 responded and 36 self-reported having first-degree relatives with symptoms related to spondyloarthropathies. All together, 144 of 150 first-degree relatives of these 36 probands were examined for clinical and radiographic characteristics. HLA typing for HLA-B27 was performed by standard microlymphocytotoxicity method.

***Results.*** The disease duration of the 36 probands was 5.03 ± 3.76 years (0.5–14 yrs). Forty seven first-degree relatives of the 36 probands were diagnosed as having AS. The prevalence of AS among the first-degree relatives of these 36 aggregated families was 31.3%. The overall prevalence of AS among the first-degree relatives in these 402 families was estimated to be 2.8%. The recurrence risk of the first-degree relatives within these aggregated families was 31.3%, suggesting an excess risk to them of 120.4, while it was 10.8 to the general families. The probands more often had peripheral arthritis and enthesopathies ($p < 0.001$ and $p = 0.01$, respectively) than the AS patients among the first-degree relatives. HLA-B27 was associated with development of AS in the probands and the patients among the first-degree relatives.

***Conclusion.*** Although familial aggregation of AS in southern China is uncommon in general, the recurrence risk of the first-degree relatives of AS probands within the aggregated families is extremely high, according to our study among hospital based patients. As the disease of the first-degree relatives is often mild and atypical, familial background analysis should be encouraged to assist early diagnosis. (J Rheumatol 2001;28:550–3)

*Key Indexing Terms:*
ANKYLOSING SPONDYLITIS FAMILY AGGREGATE HLA-B27

The strong association of HLA-B27 with ankylosing spondylitis (AS) and other spondyloarthropathies (SpA) has been known for a long time, but other genetic and environmental components have also been suggested to play a role in the development of AS[1]. Preliminary epidemiological studies have shown the prevalence to be 0.26% in both northern and southern areas of China[2]. This is similar to the published data (0.1–0.4%) from other parts of the world[3]. Interestingly, the prevalence of AS among the HLA-B27 positive first-degree relatives of AS probands has been reported to be as high as 24%[4]. We evaluated the recurrence risk of developing AS among the first-degree relatives of 36 AS probands. We also studied the clinical and some laboratory characteristics of the disease among these probands and their first-degree relatives with AS.

## MATERIALS AND METHODS

*Patients.* Questionnaires were sent to 473 patients with AS hospitalized or treated in the outpatient department of Nanfang Hospital during 3 years (1994–1997). These patients were diagnosed to have AS according to the modified New York criteria[5]. Out of 473 patients contacted, 402 responded (responder rate 85%), and 36 (8.96%) self-reported to have at least one first-degree relative who had chronic low back pain, arthritis, or other manifestations of SpA. Asymptomatic individuals were regarded as unaffected. The 36 affected families were unrelated and none had definite knowledge of the consanguinity of their parents. All first-degree relatives within the 36 families (n = 150) were invited by mail to participate in this study; 144 of them responded and agreed to participate. (Six first-degree relatives were not available to participate in the study at due time. They were 4 sons, one mother, and one daughter, and there was no evidence to suggest the AS diagnosis among them according to the probands or other family members.) The completion rate was 96%. All 144 first-degree relatives were interviewed for symptoms of SpA. They all underwent an examination and measurement of their spinal movement (Schober test) and chest expansion at the level of the fourth intercostal space, which were performed by trained rheumatologists. Posteroanterior radiographs of the pelvis and posteroanterior and lateral radiographs of the lumbar spine were made. Sacroiliitis was graded by rheumatologists and radiologists together

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according to the New York criteria[6]. Computer tomography (CT) of the sacroiliac joint was done in 8 cases (one proband and 7 first-degree relatives) who had symptoms related to SpA, but the radiographic findings were atypical to the diagnosis of AS.

*Typing for HLA-B27.* Blood samples were collected from all 36 probands and 144 first-degree relatives, and typing for HLA-B27 was performed by standard microlymphocytotoxicity assay as described[7]. The standard antisera and standard control sera were from the Department of Immunology, Beijing 307 Hospital, Beijing.

*Statistics.* Fisher's exact test was used to evaluate statistical significance between groups. The recurrence risk (Kr) of the first-degree relatives was estimated by the method of proband exclusion[8]: Kr = (R – N)/(T – N), where R is the number of the affected persons in aggregated families, N is the total number of the aggregated families, and T is the total number of the probands and first-degree relatives included in the aggregated families. The excess risk ($\lambda_r$) to the first-degree relatives was estimated according to a published method[9]: $\lambda_r$ = Kr/K, where Kr is the recurrence risk of first-degree relatives and K is the prevalence of AS in the general population.

## RESULTS

Thirty-six of 402 patients with AS (8.96%) self-reported a positive family history. The disease duration of these 36 probands was 5.03 ± 3.76 years (0.5–14 yrs). Among 144 first-degree relatives of these 36 probands, 47 were diagnosed as typical AS according to the modified New York criteria[5], the prevalence being 31.3% (47/150). Of these, 42 were male and 5 female (M:F = 8.4:1). If the 36 probands and their first-degree relatives with AS were combined, the prevalence of AS in this special population would reach 44.6% (M:F = 10.8:1). If the first-degree relatives in all families (including families with or without other affected members) were estimated according to the aggregated families, the prevalence in general families in southern China would be 2.8% [150/36 = 4.17, 47/(402 × 4.17) = 0.028]. Considering all the 47 diagnosed AS patients among the first-degree relatives, 27 were fathers, 15 were siblings, and 5 were children of the probands. The mean age of the probands and the first-degree relatives was 26.44 ± 10.6 and 40.9 ± 13.3 years, respectively ($p < 0.001$). The age distributions among probands and first-degree relatives are shown in Table 1. The age of the majority of the probands (72.2%) was under 36 years, but a majority of patients with AS among the first-degree relatives (70.2%) was ≥ 36 years. The recurrence risk of the first-degree relatives in these 36 aggregated families was 31.3%, which is substantially higher than the prevalence in the general population (0.26%). This suggests an excess risk to the first-degree relatives within these aggregated families of 120.4, while the excess risk in general families is 10.8.

*Table 1.* Age distribution of probands and first-degree relatives with AS.

| Age, yrs | Probands, n = 36 | First-degree Relatives, n = 47 | p |
|---|---|---|---|
| | n (%) | n (%) | |
| ≤ 16 | 8 (22.2) | 2 (4.2) | |
| 17–35 | 18 (50.0) | 12 (25.5) | < 0.001 |
| ≥ 36 | 10 (27.8) | 33 (70.2) | |

The clinical and laboratory data of 36 probands and their 47 affected first-degree relatives are compared in Tables 2 and 3. The prevalence of peripheral arthritis and enthesopathy among the probands was markedly higher than in the AS cases among the first-degree relatives ($p < 0.001$, $p = 0.01$, respectively), but the symptoms of low back pain and motion limitation of the lumbar spine were similar in these 2 groups (Table 2). Sacroiliitis detected on radiographs tended to be milder among the first-degree relatives (Table 3). In addition, out of 8 persons with chronic low back pain and/or arthralgia but without typical radiographic sacroiliitis, 3 cases were confirmed to have sacroiliitis according to

*Table 2.* Clinical characteristics of probands and first-degree relatives with AS.

| | Probands, n = 36 | First-degree Relatives, n = 47 | p |
|---|---|---|---|
| | n (% ) | n (%) | |
| Low back pain | 36 (100.0) | 47 (100.0) | 1.00 |
| Peripheral arthritis | 29 (80.6) | 16 (34.0) | < 0.001 |
| Enthesopathy | 25 (69.4) | 19 (40.4) | 0.01 |
| Schober test | 34 (94.4) | 39 (82.9) | 0.17 |
| Chest expansion | 10 (27.8) | 21 (44.7) | 0.16 |

*Table 3.* Laboratory characteristics of probands and first-degree relatives with AS.

| Laboratory Data | Probands, n = 36 | First-degree Relatives, n = 47 | p |
|---|---|---|---|
| | n (%) | n (%) | |
| HLA-B27+ | 35 (97.2) | 43 (91.5) | 0.38 |
| Rheumatoid factor– | 36 (100.0) | 47 (100.0) | 1.00 |
| Sacroiliitis radiographic grade | | | |
| II | 7 (19.4) | 19 (40.4) | 0.05 |
| III | 20 (55.6) | 21 (44.7) | 0.37 |
| IV | 9 (25.0) | 7 (14.9) | 0.27 |

CT, and were diagnosed as AS. The sacroiliitis detected by CT was graded as degree II (as shown in Table 3), regardless that they were atypical on the radiographs.

The frequency of HLA-B27 among the probands was 97.2% and among the first-degree relatives with AS 91.5%. All together, 46.2% (43 out of 93) of the HLA-B27 positive first-degree relatives in multicase families developed AS. However, the frequency of HLA-B27 among the group of non-AS first-degree relatives is still higher than in Chinese populations (4%) in general[2].

## DISCUSSION

Familial aggregation of AS has been reported worldwide[3,10,11], but only one study is available from China[4]. In our study, 36 (8.96%) responding AS probands self-reported a positive family history. The response rate (85%) can be considered satisfactory. Thus, the family aggregation of AS does not seem to be a common event in southern China. By evaluating the clinical and laboratory data of the 144 first-degree relatives of the 36 patients with AS, we found 47 cases definitely diagnosed as AS. This frequency is more than 100 times higher than the prevalence in general populations in southern China[2]. Statistical evaluation showed that the recurrence risk of the first-degree relatives within these aggregated families was substantially higher than the population prevalence. The risk to have AS for the first-degree relatives within these aggregated families was 120 times as high as for the general population. This calculation of recurrence risk among the first-degree relatives of AS probands was based on these special families and cannot be considered as a recurrence risk among families at large in southern China. Because this study related to hospital based patients, and Nanfang Hospital is a tertiary care center for the relatively more severe cases referred from other places in southern China, the results cannot be extrapolated to Chinese patients with AS at large.

Within the aggregated families, 46% of the HLA-B27 positive first-degree relatives developed AS. That only the first-degree relatives within the aggregated families of AS were included in our study contributes to this high prevalence. However, a French study showed similar results. They reported that 49/85 (58%) of HLA-B27 positive members from 17 families were found to have SpA[12]. Van der Linden, *et al*[3] have reported that among individuals 45 years or older, 21% of HLA-B27 positive first-degree relatives of randomly selected AS probands developed AS. The mean age of the probands in their study was 40 years, much higher than in our study (26 years), and first-degree relatives younger than 15 years were excluded from their study. In this study, probands younger than 20 years usually have only 2 first-degree relatives (parents) because China has had the one-child policy for over 20 years. It might also contribute to the high occurrence of AS. A relatively high number of HLA-B27 positive probands also have HLA-B27 positive parents. This could result in them having a higher genetic load effect and being more likely to develop AS, as proposed by Calin, *et al*[11].

The clinical symptoms were more severe among the probands than among the first-degree relatives. The probands showed an increased frequency of peripheral arthritis and enthesopathies (which are considered to reflect disease activity). The first-degree relatives with AS more often had second grade sacroiliitis than the probands (the grade of sacroiliitis is often considered clinically to be the index of disease severity). Thus, the disease of the first-degree relatives seemed to be milder than that of the probands, which revealed a possible reason why 1/3 (15/47) of the first-degree relatives with AS had never seen the doctor before this survey. So due to atypical and milder symptoms the AS diagnosis was delayed in 1/3 of the cases among the first-degree relatives (as long as 7 years in one case) until our survey. This would also be the reason why the probands were probands. They had the severe disease and therefore had a greater chance of being diagnosed, and also a greater likelihood of being hospitalized. Calin, *et al*[13] also reported that the familial cases with AS had milder disease compared to the sporadic cases. They suggested that familial cases had more susceptibility genes and fewer severity genes.

In this study, the frequency of HLA-B27 among the first-degree relatives in the 36 families studied (64.5%) was much higher than in the general population (4%)[2], and nearly half of the HLA-B27 positive first-degree relatives had AS, supporting again the importance of HLA-B27 for the development of AS. It is not known whether the distribution of HLA-B27 subtypes among Orientals has an influence on this high prevalence of AS among first-degree relatives. The HLA-B*2704 subtype is the predominant subtype among Orientals, whereas HLA-B*2705 is predominant among Caucasians[14-16]. Calin, *et al*[12] reported that AS was more prevalent among children and siblings of female index cases than among those of male cases. Children of female cases with a young age at onset had a higher incidence of AS than children of men with similar age of onset. This evidence suggests the importance of additional factors. Khan, *et al*[17] have reported HLA-B7, HLA-Bw22, or HLA-B40 in 62% of HLA-B27 negative Caucasian patients with Reiter's syndrome, AS, and sacroiliitis. Obviously, other genetic factors in addition to HLA-B27 also influence the development of AS. The same environment and lifestyle, and probably similar normal flora in the gut could also contribute to the familial aggregation of AS.

The high frequency of AS among first-degree relatives should remind physicians that careful inquiries regarding the family members of patients with AS should be made. Typing for HLA-B27 and/or radiographic studies of the pelvis among first-degree relatives, especially the men, would assist early diagnosis in patients with atypical symptoms.

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