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Citation for published version (APA):
Mardjuadi, A. (1999). HLA-B27 associated rheumatologic diseases in Indonesia

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Chapter 4

Evidence that HLA-B*2706 is not protective against spondyloarthropathy
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ABSTRACT:

Objective. Studies in Southeast Asia showed that HLA-B*2704 is positively associated with spondyloarthropathy (SpA), while B*2706 does not occur in such patients. In view of the absence of an association between B*2706 and SpA it was suggested that B*2706 protects against the disease, while it is supposed that B*2704 presents pathogenetic peptides. We studied families in which both B*2704 and B*2706 occurred to see whether in B*2704/B*2706 heterozygotes the effect of one of the subtypes shows a preponderance over the other.

Methods. Two families of mixed Chinese/Indonesian origin were studied. HLA-B27 subtyping was performed by polymerase chain reaction in combination with sequence specific oligonucleotide probes.

Results. In one family, members with B*2704, B*2706 or both occurred. In the other family B*2704, B*2706 and B*2708 were present. In both families SpA was only seen in B*2704 positive members, while the B*2706 and B*2708 positive members were healthy, except some B*2704/B*2706 or B*2704/B*2708 heterozygotes.

Conclusion. The pathogenic influence of B*2704 is thus dominant over the supposed protective influence of B*2706. It is probable that B*2704 can present pathogenetic peptides, while a protective influence of B*2706 does not exist. B*2708, which was until now only described in a few cases, behaved in this study as B*2706 and is probably not associated with SpA. (J Rheumatol 1999; 26: in press)

Key Indexing Terms:

SPONDYLOARTHRITIS
HLA-B*2704
HLA-B*2706
FAMILY STUDY
HLA-B*2708

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Supported by the Nationale Reumaprijs 1996 of the Netherlands

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The strong association between HLA-B27 and spondyloarthropathy (SpA) points to a pathogenetic role of this molecule. Within HLA-B27 now twelve subtypes are described (HLA-B*2701 to HLA-B*2712). These subtypes differ among each other by only a few amino acid residues in the peptide binding groove. Studies in Indonesia, Thailand and Singapore revealed that in contrast to B*2704, B*2706 is not associated with SpA. It was suggested that B*2706 might protect against the disease.

The subtype B*2706 differs from the other subtypes by its unique highly negatively charged aspartic acid at position 114. This position forms the rim between the D and the E pocket. The highly negative charge might prevent the fitting of the positions 3 and/or 7 of "pathogenetic peptides" in the D and/or E pocket, while such peptides might prefer the positively charged histidine, which is present in most positively associated subtypes at this position.

In this family study we investigated whether in B*2704/B*2706 heterozygotes the disease predisposing subtype B*2704 or the subtype B*2706 which was suggested to be protective is relevant for the final clinical outcome.

**MATERIALS AND METHODS**

Two families of mixed Chinese/Indonesian origin were studied. Of one family most members lived in North Holland in the Netherlands, of the other family most members lived in Middle Java in Indonesia. The diagnosis SpA was made according to the criteria of the European Spondyloarthropathy Study Group (ESSG). B27 subtyping was performed by polymerase chain reaction in combination with sequence specific oligonucleotide probes as described earlier.

**RESULTS**

The family mainly living in the Netherlands in which B*2704 and B*2706 occurs is depicted in Figure 1. The family mainly living in Indonesia, in which B*2704, B*2706 and B*2708 occurs is shown in Figure 2. From these figures it is clear that SpA was only seen in the members with B*2704 - all B*2704 negative members were healthy. In each family the B*2704/B*2706 heterozygote member had SpA. B*2706 positivity does therefore not protect against this disease. In the family depicted in Figure 2 there were two B*2704/B*2708 heterozygote members. Both had SpA.

**DISCUSSION**

The present family study shows that B*2706, although not being associated with SpA, does not protect against this disease in the presence of B*2704. The pathogenic influence of B*2704 is thus dominant over a supposed protective influence of B*2706. It is probable that B*2704, in contrast to B*2706, can present pathogenetic peptides. This pathogenic activity is not influenced by B*2706. This situation differs thus principally from the observations in insulin dependent diabetes mellitus where DQB1*0602 is protective.

B*2708 behaves in this study exactly as B*2706. Since all B*2708 positive members, except the B*2704/B*2708 heterozygotes, were healthy, it is possible that B*2708, like B*2706, is negatively associated with SpA. Whether this is really so should be the subject of population studies. B*2708 was until now described only in a few caucasian cases. That this subtype is so rarely seen might be due to the fact that is easily missed, since subtyping is mostly only performed on HLA-B27 positive persons, while the classical serological HLA typing methods type B*2708 as HLA-B7. Whether
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B*2708 is frequent among Chinese or Southeast Asians may be studied in future.

![Figure 1](image1.png)

**Figure 1.** A Chinese/Indonesian family of which most members live in the Netherlands. One man (number 4, shaded), being B*2704/B*2706, has spondyloarthropathy with inflammatory spinal pain. X-ray examination of the sacroiliacal joints showed a bilateral sacrolitis with ankylosis and sclerosis. The respiratory excursion was only 3 cm. The Schober test was good (7 cm). He had attacks of acute anterior uveitis. All other members were healthy. The ages of the numbered family members were: 1, 77 years, 2, 70 years, 3, 47 years, 4, 44 years, 5, 41 years, 6, 11 years, 7, 10 years, 8, 9 years. Neg = B27 negative by serological typing method.

![Figure 2](image2.png)

**Figure 2.** A Chinese/Indonesian family of which most members live in Indonesia. Spondyloarthropathy occurs in two women and two men (numbers 1, 2, 4 and 6, all shaded) all being B*2704 positive. The family members numbered 1, 2 and 4 had inflammatory spinal pain, while number 6 had a full blown ankylosing spondylitis. All other members were healthy. The ages of the numbered family members were: 1: 66 years, 2: 44 years, 3: 47 years, 4: 42 years, 5: 35 years, 6: 40 years, 7: 40 years, 8: 22 years, 9: 20 years, 10: 15 years, 11: 8 years, 12: 10 years. Pos = B27 positive, subtyping not performed. Neg = B27 negative by serological typing method (number 8 is probably B*2708). † = family member deceased, with supposed subtypes.
REFERENCES


