

# Immunobiology

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## Original Papers

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### Organization, Sequence and Expression of the HLA-B27 Gene: A Molecular Approach to Analyze HLA and Disease Associations

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#### Abstract

Among the numerous autoimmune diseases associated with various HLA alleles, the one with the highest relative risk so far reported has been ankylosing spondylitis with HLA-B27. To examine this relationship more directly, we have cloned the gene encoding the HLA-B27 antigen and determined its complete DNA sequence. Comparison of the HLA-B27 sequence with that of the allelic HLA-B7 shows a high level of homology. Mutations are distributed evenly between exons and introns. Exon 1 and intron 1 are the most divergent ones, and the degree of divergence distinctly declines towards the 3' end. The HLA-B27 gene when transfected into murine L cells is expressed on the cell surface and reacts with a panel of monoclonal antibodies directed against monomorphic and polymorphic determinants associated with HLA-B27 antigen.

The isolation of this gene allows for the first time a search for structural features which make the HLA-B27 antigen a high risk genetic factor for a group of rheumatoid disorders, in particular ankylosing spondylitis.

#### Introduction

Among the numerous HLA markers associated with various human diseases, the HLA-B27 antigen is a clear exception. This allelic glycoprotein, present in the cell membrane of all nucleated cells, represents an unusually high-risk factor for its carriers, conveying susceptibility for a group of joint diseases of which ankylosing spondylitis (AS) is the most prominent. Pooling all data on Caucasians, one arrives at a relative risk of more than 70.0 for individuals carrying the HLA-B27 antigen (1). Recent

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*Abbreviations:* AS = ankylosing spondylitis; bp = base pair; kb = kilo bases; mAb = monoclonal antibody; T<sub>c</sub> = cytotoxic T cell; tk = thymidine kinase.

studies have been directed towards elucidating the biochemical structure of the HLA-B27 antigen (2, 3). So far, no differences between the HLA-B27 antigens present in healthy and AS patients have been found. Even the subdivision of HLA-B27 into several antigen subtypes (4) did not indicate any structural differences between the HLA-B27 molecules from healthy and affected individuals.

In order to investigate the mechanisms of HLA involvement in disease, in general, and the nature of the HLA-B27 and AS association in particular, we isolated the gene encoding the HLA-B27 antigen. In this paper we describe the expression of the HLA-B27 gene in murine L-cells and present the complete DNA sequence of the gene encoding the HLA-B27 polypeptide together with its deduced complete amino acid sequence. The genomic organization of the HLA-B27 gene is compared with a cross-reactive allele, the homologue HLA-B7 gene, which exhibits no significant disease association.

## Materials and Methods

### *Isolation of the HLA-B27 gene*

A genomic library was constructed with the vector pTCF (5, 6) from peripheral white blood cells of a healthy individual with the HLA type: HLA-A2/2, -B5/27, -Cw2/3. The cosmid library was screened with an HLA-B locus specific cDNA probe derived from the 3' untranslated region of the HLA-B8 gene (7).

### *DNA sequence analysis*

DNA sequence analysis of the three Bg1II fragments containing the entire HLA-B27 gene subcloned in the vector pUC13 was carried out mostly by the dideoxy sequencing method (8) and partly, to verify ambiguous nucleotides, by the chemical sequencing procedure (9). The sequencing strategy is shown in Figure 1.

### *Transfection of cosmid clone CD2.6 into murine Ltk<sup>-</sup> cells*

Murine thymidine kinase negative (tk<sup>-</sup>) cells, LD1 (H-2<sup>b</sup>) were transformed with cosmid DNA and the herpes tk gene contained in the vector pOPF (5), using the calcium phosphate-mediated DNA transfer technique (10). Populations of transformed cells were selected using hypoxanthine-aminopterin-thymidine (HAT) selection, and stable Ltk<sup>+</sup> transformed clones were established. The human lymphoblastoid cell line LG-2 (HLA-A2,2; B27/27; Cw1/1) was used as a positive control for HLA-B27 expression.

### *Monoclonal antibodies (mAb)*

The origin and characteristics of the mAbs used are listed in Table 1.

### *Immunofluorescence staining and cytofluorography*

Cell surface antigen expression by L cells was studied by EPICS analysis (EPICS V, Coulter Electronics). Monolayer cultures of L cells were harvested by 1 mM PBS/EDTA and washed three times in PBS, 0.1 % Na Azide, 10 % FCS. Approximately 10<sup>5</sup>-10<sup>6</sup> cells were incubated with 50 µl of culture supernatant or ascitic fluid (1:10<sup>3</sup>) of monoclonal antibodies. After 1-h

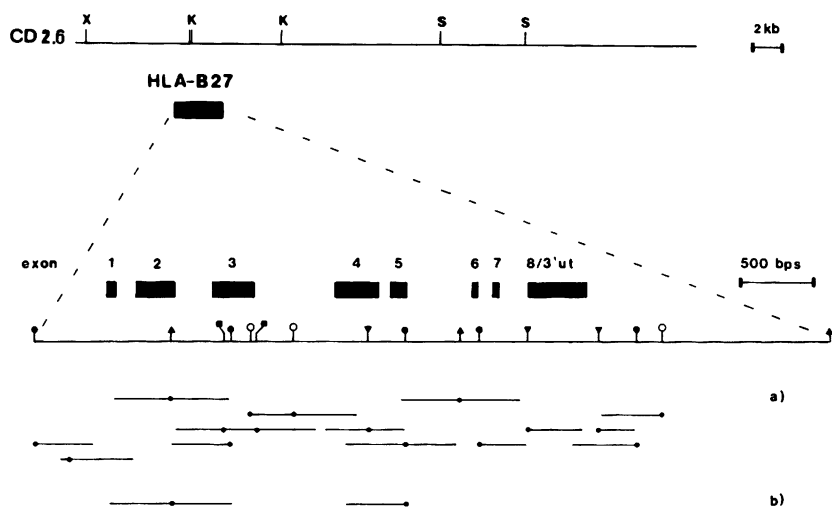


Fig. 1. Restriction map of the cosmid clone CD2.6, fine restriction map of the HLA-B27 locus and sequence strategy.

Top line: Restriction map for the cosmid clone CD2.6 encoding the HLA-B27 antigen. The following restriction sites are shown: K = KpnI; S = SalI; X = XhoI. Middle line: The fine restriction map of the HLA-B27 locus.  $\uparrow$  = BglII;  $\blacksquare$  = KpnI;  $\circ$  = PstI;  $\nabla$  = PvuII;  $\bullet$  = SacI. Above the restriction map is shown the position of the exons and the 3' untranslated region (3' ut).

a) sequences determined by the dideoxy sequencing method (8).

b) sequences obtained by the chemical sequencing procedure (9).

incubation, cells were washed and stained with 50  $\mu$ l of fluorescein-conjugated goat anti-mouse IgG + IgM (Jackson ImmunoResearch Laboratories, Inc.). Fluorescence intensity was measured by flow microfluorimetry by analyzing  $1-2 \times 10^4$  stained cells. Fluorescence data for the expression of HLA-B27 antigen on the transfected L cells are expressed as fluorescence intensity relative to the L cell of the native H-2<sup>k</sup> phenotype.

Table 1. Characteristics of the monoclonal antibodies used

Monoclonal* antibodies	Ig class	Specificity	References
W6/32	IgG2a	anti HLA-A,B,C	20
11-4.1	IgG2a	anti H-2 <sup>k</sup>	21
MPC11	IgG2b	undefined	22
KT1	IgM	anti HLA-A	23
MA2.1	IgG <sub>1</sub>	anti HLA-A2, B17	24
ME1	IgG <sub>1</sub>	anti HLA-B7, B27, B22	25
BB7.1	IgG <sub>1</sub>	anti HLA-B7	26
B27M2	IgM	anti HLA-B27, Bw47	2

\* Monoclonal antibodies ref. 20-26 were derived from culture supernatants and were gifts from Dr. J. P. Johnson. Antibody B27M2 (Ascites,  $1:10^3$ ) was a gift from Dr. F. C. Grumet.

## Results

### *Genomic organization of the HLA-B27 gene*

The entire HLA-B27 gene is contained in the cosmid clone CD 2.6. The restriction map of the cosmid clone and the gene, itself contained in three BgIII fragments, is shown in Figure 1. No other class I gene was located within a distance of 6 kb to the left side and of 30 kb to the right side of the HLA-B27 locus. Since this cosmid clone contains only one HLA class I gene, it was used directly for the gene transfer experiments.

### *Expression of the human HLA-B27 antigen in murine cells transformed with the cloned HLA-B27 gene (CD2.6)*

We have introduced cosmid CD 2.6 (see Fig. 1) together with the herpes simplex virus thymidinekinase (tk) gene into mouse L tk<sup>-</sup> (of H-2<sup>k</sup> haplotype) cells using calcium phosphate DNA transfer. We tested the tk

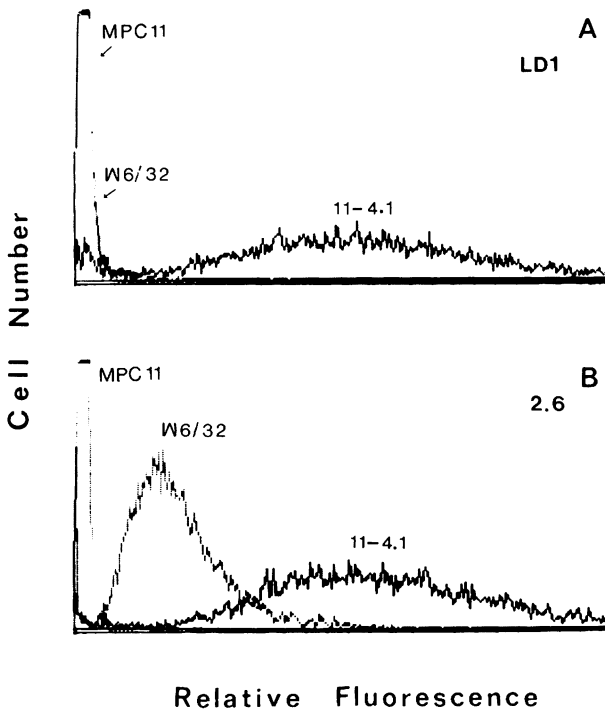


Fig. 2A and B. EPICS-Analysis: Reactivity of the LD1 cell line (Fig. 2A), and the transfection clone 2.6 (Fig. 2B) with different anti-H-2 and anti-HLA monoclonal antibodies. Fig. 2A represents the fluorescence profiles of the LD1 cell line (H-2<sup>k</sup>) with the mouse plasmocytoma antibody MPC-11 and monoclonal antibodies W6/32 (HLA-A, B, C) and 11-4.1 (H-2<sup>k</sup>). Fig. 2B shows the reactivity pattern of the transfection clone 2.6 with the same MoAbs MPC-11, W6/32 and 11-4.1. The fluorescence profiles were obtained by analysing  $2 \times 10^4$  cells. Fluorescence intensity was assessed by flow microfluorimetry by using integral amplification.

Table 2\*. Binding of anti-H-2 and anti-HLA antibodies to the mouse L cell line LD1, the mouse L cell transfectant 2.6 and the human B cell line LG-2

Cell	Antibody	Specificity	% pos. cells	Fluorescence intensity (median)
LD1	–		1.7	4.3
LD1	11-4.1	H-2 <sup>k</sup>	95.1	140.0
LD1	MPC11	undefined	3.4	5.8
LD1	W6/32	HLA-A,B,C	2	4.3
2.6	–		1.4	4.8
2.6	11-4.1	H-2 <sup>k</sup>	98.0	150.0
2.6	MPC11	undefined	2.3	5.1
2.6	W6/32	HLA-A,B,C	96.0	50.0
2.6	KT1	HLA-A	1.4	4.6
2.6	MA2.1	HLA-A2, B17	1.9	4.6
2.6	ME1	HLA-B7, B27, B22	95.0	40.4
2.6	BB7.1	HLA-B7	2.3	4.8
2.6	B27.M2	HLA-B27, Bw47	9.3	10.4
LG-2	–		3.0	9.1
LG-2	W6/32	HLA-A,B,C	88.0	173.0
LG-2	11-4.1	H-2 <sup>k</sup>	2.0	6.3
LG-2	MPC11	undefined	4.0	8.2
LG-2	KT1	HLA-A	60.0	41.8
LG-2	MA2.1	HLA-A2, B17	68.0	47.7
LG-2	ME1	HLA-B7, B27, B22	58.8	138.1
LG-2	BB7.1	HLA-B7	18.0	11.3
LG-2	B27.M2	HLA-B27, Bw47	49.5	90.0

\* The results are representative of several different experiments

positive clones for expression of HLA class I cell surface antigens, using monoclonal antibody binding in immunofluorescence assays.

The results of the binding assays are shown in Figure 2 and Table 2. All clones derived from the CD2.6 transformation bind anti-HLA class I monomorphic antibody (W6/32) at a level comparable with the endogenous H-2 antigen expression. The level of HLA antigen detected was 30–50 % of that of the H-2<sup>k</sup> antigen.

These assays demonstrate that L cells transformed with cosmid CD2.6 expressed a cell-surface polypeptide which is recognized by W6/32, while the untransformed cells were completely negative. To characterize the HLA-antigen encoded by the clone CD2.6 we used several monoclonal reagents directed against HLA antigens of the donor from whom the cosmid library was constructed (see Table 2). The HLA-A2 allele was excluded, since the monomorphic anti-HLA-A monoclonal antibody, KT1, and monoclonal antibody MA2.1, which reacts with HLA-A2, did not bind to the transfectant clones (or gave signals comparable to the MPC11 control). The cosmid clone CD2.6 did bind, however, two monoclonal

antibodies directed against HLA-B27. The reagent ME1 binds to the transfectants at the same level as W6/32. This binding is not due to cross-reactivity with HLA-B7, since binding of BB7.1 was negative. The monoclonal antibody B27.M2, which recognizes a subset of HLA-B27 antigens, also binds to the transfectant clones, although at a much lower level. This reagent is strongly positive for a B cell line derived from the individual from whom CD2.6 was isolated. The lower binding of this mAb to the transfected L cell may be due to the combination of xenogeneic  $\beta_2$  microglobulin with the HLA-B27 polypeptide. The expression of transfected HLA-B27 gene in the murine cells is increased twofold after incubation with lymphokines present in a supernatant derived from rat spleen cells stimulated with Concanavalin A (data not shown). These data show that cell lines transformed with cosmid CD2.6 express a cell-surface antigen with a specificity which is indistinguishable from the HLA-B27 antigen of the positive control B cell line LG-2 (HLA-A2,2; B27/27). We therefore conclude that the clone CD2.6 codes for the HLA-B27 antigen.

We tried to determine whether the presence of the HLA-B27 molecule on the murine cells could render these cells as targets for allogeneic cytotoxic T cell ( $T_c$  cell)-mediated killing by human  $T_c$  cells raised against the HLA-B27 antigen. Thus far, however, human anti-B27  $T_c$  cells did not lyse the transfectant L cell clones significantly (data not shown). It was reported previously that murine L cells expressing HLA class I genes are poor targets for human allogeneic  $T_c$  cells (11, 12), whereas other transfected murine cells expressing HLA class I antigens can be lysed by human allogeneic  $T_c$  cells (12).

### *General structure of the HLA-B27 gene*

The overall structure and dimensions of the HLA-B27 gene are the same as those of other reported HLA genes. The HLA-B27 gene consists of eight exons and seven introns. Table 3 shows that the majority of the exons are of the same length as those of the HLA-B7 (14) and HLA-A2 (14, 15) genes. The sequence of cloned HLA-B27 cDNA derived from the LG2 line, which we reported recently, confirms these exon assignments (16). The approximate size of the introns is the same in all three genes, with only minor variations in the exact lengths.

### *DNA sequence of the HLA-B27 gene*

We determined the DNA sequence of the entire HLA-B27 gene. The sequencing strategy is shown in Figure 1. The complete DNA sequence together with the deduced amino acid sequence of the HLA-B27 antigen is shown in Figure 3.

The sequence of the HLA-B27 gene is similar to that of other human class I genes reported earlier (14–19). For the first time, determination of the exact length of exon 1 could be made from the sequence of this HLA-



Table 3. Sequence comparison of class I genes

Region	Length (bp)			% divergence <sup>a</sup>			H-2K <sup>b</sup> /H-2K <sup>d</sup>
	HLA-B27	B7 <sup>b</sup>	A2 <sup>c</sup>	B27/B7	B27/A2	A2/A3	
5' region	517	507	526	8.1	10.2	10.6	nd
exon 1	73	73	73	10.9	15.0	4.1	7.8
intron 1	129	123	129	9.3	12.4	10.9	3.7
exon 2	270	270	270	5.2	10.7	3.0	10.3
intron 2	241	245	240	5.4	9.5	3.3	4.3
exon 3	276	276	276	6.1	8.3	4.7	11.2
intron 3	575	575	599	1.0	15.8	7.7	4.0
exon 4	276	276	276	0.4	10.1	4.0	6.1
intron 4	92	92	97	1.1	20.6	3.1	4.7
exon 5	117	117	117	0.8	14.5	2.6	5.8
intron 5	442	442	436	2.2	14.5	5.0	3.9
exon 6	33	33	33	0	12.2	3.0	6.0
intron 6	106	106	142	1.9	16.9	2.1	2.3
exon 7	48	48	48	0	12.5	2.1	2.6
intron 7	182	182	169	2.7	23	4.7	1.8
8+ 3' ut	424	422	405	1.8	nd	0.5 <sup>c</sup>	5.0
3' flanking	209	209	160	1.9	nd	5.5	4.0

<sup>a</sup> Insertions and deletions were counted as one change

<sup>b</sup> The sequence of Biro et al. (14)

<sup>c</sup> The sequence of Koller et al. (15)

<sup>d</sup> The comparison of Weiss et al. (29)

<sup>e</sup> Calculated for 165 bps of the HLA-A2 gene

nd = not determined

B27 gene. All other HLA class I genes published to date contain two in frame initiation codons (see Fig. 4) which would result in two possible leader peptides of 21 and 24 amino acids. HLA-B27 contains only the first ATG with an exon 1 of 49 base pairs. The gene contains the 3.5 kb Taq I fragment, a previously described restriction fragment length polymorphism which was assigned to the HLA-B27 gene (27). The fragment was detected by using an HLA class I cDNA probe. The Taq I fragment spans the 3' half of the HLA-B27 gene. The detection of this HLA-B27-specific gene band becomes easier when a probe derived directly from this region or an HLA-B locus specific probe is used.

*Potential Alternative Splicing Signals in the HLA-B27 gene.* Recently, an alternative intron/exon organization affecting the second exon has been proposed for the H-2K<sup>d</sup> gene (28). In a cDNA clone, apparently derived from a processed H-2K<sup>d</sup> transcript, an alternative splice acceptor site in the first intron, 50 nucleotides 5' to the usual acceptor site, is used. In addition, an extra intron is created by the splicing out of a DNA segment of exon 2, coding for the amino acids 6–38 of the classical H-2K<sup>d</sup> antigen. Until now it could not be shown whether this alternative splice site is used *in vivo* yielding a polypeptide that is synthesized from this alternative mRNA transcript.

GAGCTCACTCTGGCATCAAGTTCCCTCGGTACGTTTCCCTACACAGATCCAAAGCAGAGGTAAGGATGAGAGCCAGGGGATCCAGTTCCAGGGAGAGTGAAGGGAAAGCCGGCTGGCCCACTGGCC 150  
 CTCTCCCTGGTCTCCACAGACAGATCCCTTGTGCCGACTCAGGCAGACAGTGTGACAAAGAGCGTGTGTAGGAAAGAGGGATACGGAGCAACAGCTCCAAAGCCCGCCGGCCGGTCTCAGGGTCTCAGCCCTCCAGAGAGCCATTCCTCC  
 ATTGGGACGGCCAGCTTGGGGAATCCCCCACTCCACAGACTTTCACCTTCTTCTCCCAACCTATCTGGCGGTCTTCTTCCACGATATGCTGTGACCGCTCCCAATTTCCCACTCCGATGGGTGCAGGAAAGCCATTCAGTC 450

Met Arg Val Thr Ala Pro Arg Thr Leu Leu Leu Leu Leu Trp Gly Ala Val Ala Leu Thr Glu  
 TCCCGGGGGTCCCACTTCTAAATGCCACGCCACCCACCCGGAGTCAAGATTCCTCTCAGACGCCGAG ATG GCG CTC ACC GCG CCC CCA ACC CTC CTC CTC CTC CTC TCG GCG GCA GTG CCC CTG ACC GAG 580

Thr Trp Ala G 1y Ser  
 ACC TGG GCT G GTGAGTCCGGGGTCAAGCAGGAAAATGGCTCTCTGGGGAGGAGCCAGGGGACCGAGCCGGGGGCGCCAGCCCGGGGAGCCCGCCGGCAGGAGGTCGGCGGGTCTCAGCCCTCTCCCGCCAGG GC TCC 724

His Ser Met Arg Tyr Phe His Thr Ser Val Ser Arg Pro Arg Gly Glu Pro Arg Phe Ile Thr Val Gly Tyr Val Asp Asp Thr Leu Phe Val Arg Phe Ala Ser Asp Ala  
 CAC TCC ATG AGG TAT TDC CAC ACC TCC GTG TCC GGG CCC GGC CCG GAG GAG CAC CCC GGC TTC ATC ACC GTG GGC TAC GTG GAC GAC ACC CTG TTC CTG AGG TTC GAG ACC GAG ACC 838

Ala Ser Pro Arg Glu Glu Pro Arg Ala Pro trp Ile Glu Gln Glu Gly Pro Glu Tyr Trp Asp Arg Glu Thr Gln Ile Cys Lys Ala Lys Ala Gln Thr Asp Arg Glu Asp Leu  
 CCG ACT CCG AGA CAG CAG CCC CCG CCG TCC ATA CAG CAG CAG CCG CCC GAG TAT TDC CAG CCG GCG CAG ACA CAG ATC TCC AAG CCC AAG CCA CAG ACT CAG CCA GAG CAG CTC 952

Arg Thr Leu Leu Arg Tyr Tyr Asn Glu Ser Glu Ala G  
 CCG ACC CTG CTC CCG TAC TAC AAC CAG AGC GAG GCC G GTAGTACGCCCGCCCGGGCGAGGTCAAGACTCCCACTCCCCACAGTCCGGCCGGTCCCGGGTCCGAGATCCCGCCCGAGGGCC 1089  
 CCGGACCCGCCACGCCCTCCAGCCGAGAGCCCAAGCCCGCTTACCCCGCTTCAATTTTCAGTTGAGCAAAATCCCGCCGTTGCTGGGGCGGGCGGGCTCGGGGGAGCAGCCGGCTGACCCCGGGCGGTCTCAG

1y Ser His Thr Leu Gln Asn Met Tyr Gly Cys Asp Val Gly Pro Asp Gly Arg Leu Leu Arg Gly Tyr His Gln Asp Ala Tyr Asp Gly Lys Asp Tyr Ile Ala Leu Asn Glu  
 GG TCT CAC ACC CTC CAG AAT ATG TAT GGC TGC GAC GTG GCG CCG GAC GGC CCC CTC CTC CCG GCG TAC CAC CAG GAC CCC TAC GAC GGC AAG GAT TAC ATC GCC CTC AAC GAG 1343

Asp Leu Ser Ser Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr Gln Arg Lys Trp Glu Ala Arg Val Ala Glu Gln Leu Arg Tyr Leu Glu Gln Leu Cys Val Glu  
 GAC CTG ACC TCC TGG ACC GCC CCG GAC ACC CCG GCT CAG ATC ACC CAG CCC AAG TGG GAG CCC GCG CCT CTC GCG CAG CAG CTC AGA GCC TAC CTC GAG CCG CAG TCC CTC GAG 1457

Trp Leu Arg Arg Tyr Leu Glu Asn Gly Lys Glu Thr Leu Gln Arg Ala A  
 TGG CTC CCG AGA TAC CTC GAG AAC GGG AAG GAC CCG CTC CAG CCG GCG G CTACAGGGGCGACTGGGGAGCCTTCCCACTCCTCTAAGTCCCGGGGATGGCCCTCCACAGAAAGAGGAGAAAATGGCATC 1500  
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sp Pro Pro Lys Thr His Val Thr His His Pro Ile Ser Asp His Glu Ala Thr Leu Arg Cys Trp Ala Leu Gly Phe Tyr Pro  
 AGAGATGCAAAAGCCGCTGAATTTTCTGACTTCTCCCACTCAG AC CCC CCA AAG ACA CAC CTC ACC CAC CAC CCC ATC TCT GAC CAI GAG GCC ACC CTG AGG TGC TGG CCG CTC GGC TTC TAC CCT 2184

Ala Glu Ile Thr Leu Thr Trp Gln Arg Asp Gly Glu Asp Gln Thr Gln Asp Thr Glu Leu Val Glu Thr Arg Pro Ala Gly Asp Arg Thr Phe Gln Lys Trp Ala Ala Val Val  
 GCG GAG ATC ACA CTG ACC TGG CAG CCG GAT GGC GAG CAG CAA ACT CAG GAC ACT GAG CTT GTG GAG ACC ACA CCA CCA GGA GAT ACA ACC TTC CAG AAG TGG GCA GCT GTG GTG 2278

Val Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu Gly Leu Pro Lys Pro Leu Thr Leu Arg Trp G  
 GTG CCT TCT GGA GAA GAG CAG AGA TAC ACA TGC CAT GTA CAG CAT GAG GGG CTC CCG AAG CCC CTC ACC CTG AGA TGG G GTAAGGACGGGGGAGGGGTCATATCTCTCTCAGGGAAACC 2400

1u Pro Ser Ser Gln Ser Thr Val Pro Ile Val Gly Ile Val Ala Gly Leu Ala Val Leu Ala Val Val Val Ile Gly  
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1y Gly Lys Gly Gly Ser Tyr Ser Gln Ala Ala C  
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ys Ser Asp Ser Ala Gln Gly Ser Asp Val Ser Leu Thr Ala STOP  
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 CCGGGTGGGTGGCTAGTCCGAAAAGCCGTGGTAAATGGAGTTTCTTGGATGGGATCTTGGCCCTGTGTGGCTGGGCTTTAGAGTGTCTACGCTTACG TGAATCAACAGAAATTTCTCTGACTGTTCTTGTCTGAC CC TGACAG  
 AGCTGTCTTCTGGGAGTCAAGATGGAGATTTCTTCAAGCCCTCCCTTGTGACTTCAAGAGCCTTGGCATCTCTCTTCCGAAAGGCACTGATATCTCTCCGCTCCCTTAAAGATATGTGAGGAGGTCGAGAGCCAGCCCAACC  
 CCGTCTCCACTGTGACCCCTCTCCCACTGCTGACTGTGTTTCCCTCCAGTACTTTCCCTTCCAGAGAGCGGGCTGTGCTCACTCTCTCAACTTTATGTGCTGAGCTGCACTTCCCTCACTGAAATAA 3535  
 AGAATCTGAATATAAATTTGTTTCTCAATATTTGCTATGAGAGGTTGATGGATAAATAAAGTCAATTCCTGGATTTGAGAGAGCAATAAAGACCTCAGAACCTTCCAGATCTGCAATCTGGCTGTGCTGACTGTCTGGCAG  
 CTGGGGTGTGAGAAAGGCTGTGGGGGGCCAGCTGTGGAGGGCCCTTGCCCAATTTGGTGTGAGTCCATCATGGGCTTATGTGCTTAGTCTCAGCTGGCTGGCTCAGCTCACTGCTCACTGCTCACTGCTCACTGCTCACTGCT 3835  
 AGCCGGAGCTGTGACCCAGAGGCTCACAC 4015

Fig. 3. Nucleotide sequence of the HLA-B27 gene. Nucleotides are numbered from the Sac I site. The promotor (TCTAAA) and the polyadenylation (AATAAA) signals are underlined. Splice sites and potential alternative splice signals are indicated by lines. The amino acids are placed above the triplets of the exons in the three letter code.

Inspection of the HLA-B27 gene sequence reveals several alternative splice sites (AG/G) only a few of which do not result in stop codons. The alternative splice acceptor sites described for the H-2K<sup>d</sup> gene are found in exactly the same positions in the HLA-B27 gene (659 and 831, marked in Fig. 3) together with the corresponding donor site in exon 2 at position 736. The additional exon would code for 26 amino acids as in the H-2K<sup>d</sup> gene. A similar alternative transcript cannot be generated from the HLA-B7 gene. The presence of potential alternative splice signals in the HLA-B27 gene raises the question of whether they might be used. No cDNA clone coding for HLA-B27 has been described that is the product of an alternative spliced transcript (16).

A complete cDNA sequence coding for the HLA-B27 antigen (16) and potential peptide sequencing data for this antigen (3) have been published recently. We, therefore, do not discuss the protein sequence in detail. It is of interest to note that the genomic sequence for the HLA-B27 antigen contains the triplet GCG at amino acid position 182 coding for alanine, as it was found by protein sequencing (3). The cDNA clones, derived from a homozygous B cell line, code for a valine (GTG) in this position. A second amino acid replacement change is found in the leader at amino acid position 7 where the cDNA clone codes for a glutamine (GAG), due to a change of three nucleotides. Another additional nucleotide is found in the 3' untranslated region at position 3692. The insertion of a T destroys the Taq I site found in the cDNA (16). This Taq I site is in so far important, because the LG2 line from which the cDNA clones were derived cannot contain the polymorphic Taq I fragment of 3.5 kb. Its corresponding fragment must be of 1800 bp. The five changes are the only differences found between the cDNA sequence and the genomic DNA sequence. Since both genes code for the same HLA-B27 subtype (HLA-B27.1), we conclude that this might be the first evidence for somatic mutations in B cell lines in a gene other than immunoglobulin.

*Comparison of the gene sequence of HLA-B27 with an allelic gene sequence.* The comparison of the two HLA-B alleles, HLA-B27 and the cross-reactive HLA-B7, at the gene level shows a high degree of nucleotide sequence conservation in both coding (exons) and non-coding regions (introns), as well as in the flanking regions (Table 3). The highest level of divergence is expressed in intron 1 and exon 1, which is not contained in the mature HLA molecule. The degree of divergence is highest in the 5' half of the gene (exon 1 to exon 3). The HLA-B27 and HLA-B7 genes are virtually identical in the 3' part of the genes. Surprisingly, the exons and introns have accumulated mutations to a similar degree.

The sequence comparison of exon 2 of the two alleles (Fig. 4) reveals that most of the mutations are scattered. Only one cluster of changes is found to the 3' end of this exon, from amino acid position 77 to 83.



## Discussion

We have shown that the cosmid clone CD2.6 contains one HLA class I gene which is the HLA-B27 gene. This human HLA gene can be expressed in murine L cells and is recognized by monoclonal anti-HLA reagents even when the heavy chain is combined with murine  $\beta_2$  microglobulin. Several monoclonal antibodies demonstrate that the epitopes, normally associated with the HLA-B27 molecule, are present on the surface of the transformed L cells.

The DNA sequence and deduced amino acid sequence of the HLA-B27 antigen were compared to the DNA sequence of its allele HLA-B7. As we have discussed elsewhere (16), the polypeptide structure exhibits some replacement changes unique to the HLA-B27 antigen. Among them two mutations are unusual: position 67 is occupied by a cysteine and position 131 by a serine. The change in position 131 generates a new restriction site, GAG CTC, which is recognized by the enzyme SacI. These changes could be decisive in the peculiar role of HLA-B27 as a risk factor for ankylosing spondylitis.

Surprisingly, the comparison of the DNA structure of the HLA-B27 gene with its allele HLA-B7 revealed a high degree of homology between the two genes. This is interesting in two aspects: Firstly, the HLA-B27/B7 pair is another example of human class I alleles showing a greater degree of nucleotide conservation than allelic class I genes in the mouse (15, 29). Thus, the two murine alleles H-2K<sup>b</sup> and H-2K<sup>d</sup> have a much lower level of homology in the polymorphic exons 2 and 3 (10.3 and 11.2 % divergence, respectively), whereas the introns show the same degree of homology as the human alleles (see Table 3). This higher mutation rate in the H-2K genes could be due to their position centrometric to the I-A region, thus possibly making it a preferred target for gene conversion events. This explanation is supported by the sequences of H-2 class I genes other than H-2K. The sequence comparison of the H-2D<sup>b</sup> gene with its proposed allele H-2L<sup>d</sup> (30) (H-2D<sup>d</sup> being less homologous) shows a level of divergence comparable to human HLA-A and HLA-B alleles. Another explanation for the fact that the human class I alleles are more similar than their murine homologues could be based on the different evolution in the two species. It remains to be explained why human class I alleles exhibit quite a high degree of divergence at the 5' half of the gene (exon 1 and intron 1).

The second aspect of interest concerns the differences found between the HLA-B27 and HLA-B7 genes. The two HLA-B alleles are as homologous as the HLA-A alleles and show to the 3' end of the gene, i.e. exon 4 to 3' untranslated region, an even higher level of homology. This fact makes it difficult to assign the cause for the association of HLA-B27 with certain diseases to particular structural features of the HLA-B27 gene. Surprisingly, the highest degree of divergence is found in exon 1 and intron 2. The leader peptide, encoded by exon 1, is cleaved off during maturation of the

HLA class I molecule. The sequence of intron 2 is not part of the mRNA and therefore not translated. Only in case of an alternative processed transcript of the HLA-B27 gene involving intron 2 could this sequence be of importance.

Several hypotheses have been proposed to explain the association of some HLA alleles with certain diseases. The isolation and expression of the gene encoding the HLA-B27 antigen allows us to address the proposed mechanism with recombinant DNA techniques. Since we isolated the gene from a so far healthy individual, we cannot rule out the highly unlikely possibility that the HLA-B27 gene of a patient might contain mutations. TRAPANI et al. (31) isolated a 3.5 kb Taq I fragment containing the 3' half of a supposed HLA-B27 gene from a spondylitic patient. The partial sequence of 180 bps, derived from intron 6-exon 7-intron 7 presented in this report, is identical to our sequence, except the G at position 3223 in intron 7 is lacking in their sequence but is contained in the HLA-B7 gene.

To examine the possibility that a putative «illness susceptibility» gene in linkage disequilibrium with HLA-B27 is responsible for the diseases associated with this antigen (the two-gene theory; see ref. 1 for review) we have begun chromosomal walking experiments starting from the HLA-B27 gene, in order to compare the organization of the HLA-B27 haplotype with other extended HLA-B loci.

The molecular mimicry hypothesis (the one-gene theory; see ref. 1 for review) postulates that the molecular structure of infectious agents are similar to those of the HLA antigens on the cell surface. *In vitro* mutagenesis experiments may be helpful in defining HLA-B27 specific epitopes that may cross-react with bacterial proteins. At present, we are converting the HLA-B27 unique replacement changes at amino acid positions 67 and 131 back to the «wildtype» configuration. Then we can analyze whether these mutations affect the overall structure of the molecule defined by monoclonal antibodies and human allogeneic cytotoxic T cells.

In summary, this paper describes the isolation of the HLA-B27 gene which, for the first time, allows the investigation of the mechanisms underlying the observed association between HLA-B27 and various diseases.

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