

Are there common human leucocyte antigen associations in juvenile idiopathic arthritis and periodontitis?

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Abstract

Aim: The aim of this study was to evaluate common human leucocyte antigen (HLA) associations in patients with juvenile idiopathic arthritis ($N = 110$), in patients with generalized aggressive periodontitis ($N = 50$) and in patients with chronic periodontitis ($N = 102$) in comparison to healthy controls (no periodontitis, no arthritis $N = 102$).

Material and methods: HLA-class I and II markers were determined using microlymphocytotoxicity test and polymerase chain reaction with sequence specific primers. Statistical analyses were carried out by χ^2 -test and Yates' correction. If $n < 5$ Fisher's exact test was performed. In the arthritis group the influence of HLA on attachment loss was determined by using backwards logistic regression considering age, gender, smoking, plaque level, and the duration of the disease.

Results: In comparison with the controls HLA-DRB3* occurred more frequently in both females suffering from juvenile idiopathic arthritis (74.58% versus 54.54%, $p = 0.024$) and females suffering from chronic periodontitis (73.02% versus 54.54%, $p = 0.035$). Furthermore, among patients with juvenile idiopathic arthritis an increased odds ratio (OR) for attachment loss was found in subjects who expressed HLA-A*01 (OR = 4.6, $p = 0.014$) or HLA-A*01:DRB3* (OR = 4.3, $p = 0.031$).

Conclusion: HLA-DRB3* could be a common putative risk indicator for juvenile idiopathic arthritis and chronic periodontitis among females.

Key words: aggressive periodontitis; chronic periodontitis; HLA; juvenile idiopathic arthritis

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The term juvenile idiopathic arthritis (JIA) refers to persistent arthritis, episodes lasting for at least 6 weeks, and with an onset occurring before the 16th year of life (Petty et al. 1998). In several studies it has been shown that JIA could

be a risk factor for gingivitis or periodontitis. On the one hand, this relation could be caused by an increased plaque level as a consequence of poor manual dexterity with the brush due to upper limb disability (Savioli et al. 2004) or temporomandibular dysfunction (Ahmed et al. 2004). On the other hand, it has also been suggested that the association between JIA and periodontitis might be caused by a common dysregulation of the immune-inflammatory response (Miranda et al. 2003).

Various reports have indicated that periodontopathic bacteria could trigger

rheumatic diseases. Mercado et al. (2000) have shown that individuals with moderate to severe periodontitis have a higher risk for rheumatoid arthritis (RA). In patients suffering from RA specific antibodies against periodontopathic bacteria were proved in serum (Yoshida et al. 2001) as well as in synovial fluid (Moen et al. 2003). The serum level of such specific antibodies had influenced the degree of alveolar bone loss (Tolo & Jorkjend 1990). Cross-reactions between periodontopathic bacteria and human immunoglobulin (Ig)G could lead to the formation

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of autoantibodies such as the IgM rheumatoid factor (The & Ebersole 1991, 1996). Moreover, enzymes produced by periodontopathic bacteria could directly lead to an intraarticular inflammation (Rosenstein et al. 2004).

The immune response to bacteria is influenced by high human leucocyte antigen (HLA) polymorphism (Buckley et al. 1973, Greenberg et al. 1975) and individual peptide binding capability of cell surface HLA receptors (Rammensee 1995). Moreover, bacterial mimicry between bacteria and certain HLA molecules could lead to autoimmune reactions or to mechanisms of cross tolerance (Avakian et al. 1980, Welsh et al. 1980). For periodontitis (Machulla et al. 2002) as well as for JIA (Minden et al. 2001, Thomson et al. 2002), associations to HLA classes I and II alleles were reported.

On the basis of these findings we assume that periodontopathic peptides bound on certain HLA molecules could trigger rheumatic diseases such as JIA. Hence, common HLA molecules could be indicative of JIA as well as periodontitis and could be putative risk or resistance factors for both diseases.

Therefore, the first purpose of the present study was to examine whether there are any common HLA associations in patients with JIA, chronic periodontitis (CP) and aggressive periodontitis (AP) in comparison to a healthy control group having neither JIA nor periodontitis. Our second objective was to investigate whether such common HLA alleles were also a distinctive feature in JIA patients with periodontitis in comparison to JIA patients without periodontitis. Risk factor analyses for attachment loss within the JIA group were carried out considering both the duration of the JIA and established confounders for periodontitis.

Material and Methods

Patients and controls

The patient groups consisted of 110 individuals with JIA (mean age 12.1 ± 4.05 years, 53.6% females), 50 patients with AP (mean age 33.9 ± 6.5 years, 56.0% females), and 102 subjects with CP (mean age 52.1 ± 11.1 years, 61.8% females). The control group included 102 periodontitis-free individuals (mean age 61.0 ± 15.1 years, 60.8% females). All patients and

controls were unrelated Germans of Caucasian descent and were free from other general diseases known to be associated with certain HLA markers and periodontitis, respectively.

The JIA patients were treated at the Department of Paediatrics of the Martin-Luther University. The diagnosis was carried out by a specialist for rheumatology (V. J.) according to the criteria of Petty et al. (1998). Seventy-six out of 110 HLA typed JIA patients were additionally examined regarding periodontal conditions and their smoking status as previously described (Reichert et al. 2006). For periodontal examination only those JIA patients aged between 12 and 19 years were selected from the total JIA group. The minimum age was restricted to 12 years, because at this time, the period of mixed dentition is almost complete. The maximum age was restricted to 19 years because we assume that the influence of rheumatic diseases on attachment loss could be better revealed in adolescent cohorts. A 'periodontitis case' was defined as a subject who had at least one site with clinical attachment loss (CAL) > 3.5 mm. A person who smoked at least one cigarette per day was considered a smoker.

Patients with AP were evaluated from a group of 4131 patients with different forms of periodontal disease who received treatment at our Department of Operative Dentistry and Periodontology over a 4-year period fulfilling the criteria for generalized early-onset periodontitis (G-EOP) published by Tonetti and Mombelli (1998). A total of 102 cases with CP and 102 periodontitis-free individuals were selected from a group of 6800 individuals receiving dental treatment at two private dental departments for a period of 4 years. Inclusion and exclusion criteria for periodontitis patients and periodontitis-free controls have been previously described by the authors of the present study (Machulla et al. 2002).

The present study was approved by the local ethics committee and was carried out in accordance with the ethical guidelines of the 'Declaration of Helsinki'.

HLA typing

One-hundred and nine patients with JIA were typed for both HLA classes I and II alleles. In one JIA patient only HLA class I alleles were determined. The

typing of HLA class I (HLA-A, -B, and Cw) and class II alleles (DRB1, DRB3/4/5, and DQB1) was carried out by using the microlymphocytotoxic test (MLCT). In order to secure and extend the results of the serologic typing, low-resolution genomic typing with polymerase chain reaction with sequence-specific primers (PCR-SSP) was carried out as described previously (Machulla et al. 2002). Overall, 20 HLA-A, 30 HLA-B, HLA-Bw4 and Bw6, 9 HLA-Cw, 13 HLA-DRB1, HLA-DRB*3 (DR52), HLA-DRB4*(DR53), HLA-DRB5*(DR51), and 5 HLA-DQB1 alleles could be identified. Quality was verified by regular HLA typing of control samples from the Institute for Standardization and Demonstration in Medical Laboratories (INSTAND e.V., Düsseldorf, Germany) and from International DNA Exchange, UCLA Tissue Typing DNA Laboratory (Los Angeles, CA, USA).

Statistical analysis

Clinical variables such as the approximal plaque index (API) (Lange et al. 1977) and the modified sulcular bleeding index (SBI) (Mühlemann & Son 1971) were described in terms of means. The equality of variances was checked by using Levine's test. In order to compare mean values between JIA patients with periodontitis and JIA patients without periodontitis *t*-tests were performed. Differences in categorical variables were determined by χ^2 test or Fisher's exact test (if $n < 5$). HLA markers were represented as a percentage (pf%) of the total number of subjects in the group (*N*). Homozygosity was assumed if only one HLA marker was detectable within one locus. Differences in HLA phenotype frequencies were determined by χ^2 -testing and Yates' correction. If there were less than five individuals in one group who tested positive for a certain HLA allele, Fisher's exact test was carried out. As no specific hypothesis was tested, Bonferroni's correction was applied by multiplying the *p*-values with the number of comparisons tested. Logistic regression (stepwise backward elimination analysis) was used in order to determine the individual odds ratio (OR) of a striking HLA marker for periodontitis considering established confounding factors for periodontitis. In general *p*-values ≤ 0.05 were accepted as statistically significant.

Table 1. Significant HLA associations found in the JIA group in comparison to AP and CP

Total HLA-	JIA <i>N</i> = 110/ 109* pf (%)	AP <i>N</i> = 50 pf (%)	CP <i>N</i> = 102 pf (%)	Controls <i>N</i> = 102 pf (%)	JIA versus controls <i>p</i> _c	AP versus controls <i>p</i> _c	CP versus controls <i>p</i> _c
B*38	0.91	4.00	3.92	5.88	0.048	NS	NS
B*27	35.45	10.00	8.82	14.71	0.001**	NS	NS
B*37	0.00	8.00	2.94	5.88	0.011	NS	NS
Cw*01	18.18	2.00	0.00	2.94	<0.001	NS	NS
Cw*07	38.18	60.00	63.73	57.84	0.004	NS	NS
DRB1*15	16.51	22.00	35.29	34.31	0.003**	NS	NS
DRB1*16	7.34	6.00	1.96	0.98	0.022	NS	NS
DRB1*11	35.78	20.00	19.61	18.63	0.006	NS	NS
DRB5*	22.94	28.00	36.27	35.29	0.049	NS	NS
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Females	<i>N</i> = 59	<i>N</i> = 28	<i>N</i> = 63	<i>N</i> = 62	<i>p</i> _c	<i>p</i> _c	<i>p</i> _c
Cw*01	18.64	3.57	0.00	4.84	0.017	NS	NS
Cw*02	6.78	7.14	9.52	19.35	0.037	NS	NS
Cw*05	22.03	7.14	9.52	8.06	0.034	NS	NS
Cw*07	30.51	57.14	66.67	51.61	0.019	NS	NS
DRB1*11	47.46	10.71	19.05	14.52	<0.0001**	NS	NS
DRB1*07	3.39	42.86	12.70	22.58	0.002**	NS	NS
DRB3*	74.58	64.29	73.02	54.54	0.024	NS	0.035
DRB4*	28.81	67.86	31.75	46.77	0.043	NS	NS
DRB3* homoz.	28.28	10.71	12.70	11.29	0.017	NS	NS
DQB1*01	57.63	71.43	71.43	77.42	0.021	NS	NS
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Males	<i>N</i> = 51/50*	<i>N</i> = 22	<i>N</i> = 39	<i>N</i> = 40	<i>p</i> _c	<i>p</i> _c	<i>p</i> _c
B*27	62.75	9.09	12.82	10.00	<0.0001**	NS	NS
Bw4	76.47	63.64	61.54	55.00	0.033	NS	NS
Cw*01	17.65	0.00	0.00	0.00	0.004	NS	NS
Cw*02	47.06	13.64	12.82	10.00	<0.0001**	NS	NS
Bw6 homoz.	23.53	36.36	38.46	45.00	0.033	NS	NS
DRB1*01	54.00	13.64	15.38	15.00	0.041	NS	NS
DRB1*15	16.00	27.27	30.77	40.00	0.012	NS	NS
DQB1*05	42.00	27.27	30.77	20.00	0.027	NS	NS

*One patient typed only for HLA class I.

JIA, juvenile idiopathic arthritis; AP, aggressive periodontitis; CP, chronic periodontitis; pf, phenotype frequency; *p*_c (corrected by Yates or Fisher, **remained significant after Bonferroni's correction); NS, not significant; HLA, human leucocyte antigen.

Results

HLA associations found exclusively in JIA in comparison with AP and CP

In comparison with female control individuals (Table 1) the supertype HLA-DRB3* was significantly increased in both females suffering from JIA and females suffering from CP. However, there was no significance after Bonferroni's correction. The increased frequencies of HLA-B*27 (total JIA group, JIA males), HLA-DRB1*11 (JIA females), and HLA-Cw*02 (JIA males) as well as the decreased frequencies of HLA-DRB1*15 (total JIA group) and HLA-DRB1*07 (JIA females) remained significant after Bonferroni's correction.

HLA associations found exclusively in AP and CP in comparison with JIA

In the total periodontitis cohorts (Tables 2 and 3) as well as among female AP

and CP patients significant HLA associations were found. No such associations were found in the male periodontitis groups. However, none of the significant HLA associations in AP or CP patients were found in the JIA group, as well.

HLA associations in JIA patients with periodontitis in comparison with JIA subjects without periodontitis

Nineteen out of the 76 JIA patients who were examined with respect to periodontal conditions were identified as periodontitis cases. JIA patients with periodontitis showed significantly higher values of API (82.16% versus 58.60%, *p* = 0.001) and SBI (53.63 versus 29.56%, *p* = 0.002) in comparison to JIA probands without any sites with CAL. Further, compared to JIA patients without periodontitis more JIA patients with periodontitis expressed a polyarthritis (52.6% versus 26.3%,

p = 0.034). Moreover, there were no significant differences between both groups at the time of the periodontal examination with respect to the age (14.37 versus 14.46 years), the percentage of smokers (22.8% versus 15.8%), and the duration of the rheumatic disease (5.25 versus 6.26 years). Furthermore, between both groups the percentage of females was not significantly different (63.2% versus 54.4%).

In the JIA group with periodontitis the HLA alleles A*01, B*27, B*35, and DRB3*(DR52) occurred with significantly higher frequency whereas A*24 was decreased (Table 4). Moreover, the combinations HLA-A*01:B*35 and HLA-A*01:HLA-DRB3* were increased. In the JIA group the individual OR for attachment loss considering age, gender, smoking, API, and the duration of the rheumatic disease was increased by both the single allele HLA-A*01 and the combination HLA-A*01:DRB3*(R52) (Table 5 models 1 and 2).

Table 2. Significant HLA associations found exclusively in the AP group in comparison to the JIA cohort

Total HLA-	AP <i>N</i> = 50 pf (%)	JIA <i>N</i> = 110/ 109* pf (%)	Controls <i>N</i> = 102 pf (%)	AP versus controls <i>p</i> _c	JIA versus controls <i>p</i> _c
A*29	8.00	2.73	0.98	0.040	NS
A*31	0.00	5.45	8.82	0.024	NS
A*30/31	0.00	9.09	11.76	0.007	NS
DRB1*13	36.00	18.35	20.59	0.046	NS
DRBblank*	18.00	32.11	34.31	0.036	NS
Females	<i>N</i> = 28	<i>N</i> = 59	<i>N</i> = 62	<i>p</i> _c	<i>p</i> _c
A*68/69	28.57	1.69	6.45	0.007	NS
DQB1*05	17.86	33.90	43.55	0.019	NS

In males with AP no significant associations have been revealed.

*One patient typed only for HLA class I.

JIA, juvenile idiopathic arthritis; AP, aggressive periodontitis; pf, phenotype frequency; *p*_c, (corrected by Yates or Fisher); NS, not significant; HLA, human leucocyte antigen.

Table 3. Significant HLA associations found exclusively in CP in comparison to JIA. In males with CP no significant associations have been revealed

Total HLA-	CP <i>N</i> = 102 pf (%)	JIA <i>N</i> = 110/ 109* pf (%)	Controls <i>N</i> = 102 pf (%)	CP versus controls <i>p</i> _c	JIA versus controls <i>p</i> _c
A*03	19.61	24.55	32.35	0.039	NS
A*11	14.71	10.91	5.88	0.041	NS
A*29	6.86	2.73	0.98	0.032	NS
A*33	4.90	0.91	0.00	0.030	NS
B*14	5.88	1.82	0.00	0.014	NS
Cw*08	5.88	1.82	0.00	0.014	NS
Females	<i>N</i> = 63	<i>N</i> = 59	<i>N</i> = 62	<i>p</i> _c	<i>p</i> _c
B*27	6.35	11.86	17.74	0.045	NS
DQB1*06 homoz.	11.11	3.39	1.61	0.032	NS

In males with AP no significant associations have been revealed.

*One patient typed only for HLA class I.

JIA, juvenile idiopathic arthritis; CP, chronic periodontitis; pf, phenotype frequency; *p*_c, (corrected by Yates or Fisher); NS, not significant; HLA, human leucocyte antigen.

Table 4. Significant HLA deviations in patients with JIA and periodontitis in comparison to JIA individuals without any sites with CAL >3.5 mm

HLA-	JIA without CAL <i>N</i> = 57/56* pf (%)	JIA and CAL <i>N</i> = 19 pf (%)	<i>p</i> _c
A*01	22.81	52.63	0.019
B*35	14.04	36.84	0.045
A*01:B*35	1.75	15.79	0.046
A*01:DRB3*	12.50	42.11	0.009
A*24	26.32	5.26	0.044
B*27	17.54	42.11	0.040
DRB3*	58.93	84.21	0.045

*One patient typed only for HLA class I

JIA, Juvenile idiopathic arthritis; CAL, clinical attachment loss; pf, phenotype frequency; *p*_c, (*p* corrected by Yates or Fisher); HLA, human leucocyte antigen.

Discussion

For the first time, this study has focused on a common HLA background in JIA

and periodontitis. We assume that an HLA-dependent immune response to periodontopathic bacteria could influence the pathway of both diseases. The

total periodontitis group was separated in patients suffering from CP and AP because HLA deviations depend on the diagnosis among other factors (Machulla et al. 2002). Contrary to most other studies on association between HLA and periodontitis (overview: Machulla et al. 2002), in the present study the JIA and periodontitis groups were compared with control probands free from both, periodontitis and rheumatic diseases. Moreover, HLA classes I and II markers were determined using both serological and a modern molecularbiologic technique (PCR-SSP). In addition, gender dependent HLA deviations were determined. The latter have been published for periodontitis (Reichert et al. 2003) and for rheumatic diseases (James 1991). Furthermore, HLA homozygosities were taken into account. Associations with HLA homozygosities were revealed in both patients with periodontitis (Stein et al. 2003) and early rheumatoid arthritis (Goronzy et al. 2004).

The second aim of this study was to compare JIA patients with periodontitis and JIA patients without any attachment loss with respect to striking HLA markers. Following the advice for genetic studies (Loos et al. 2005), risk factor analyses were carried out considering both the duration of the JIA and established confounders for periodontitis such as age, gender, smoking, and plaque index.

The present study revealed an increased phenotype frequency of HLA-DRB3* in females suffering from JIA and females suffering from CP. However, after Bonferroni's correction these associations lost their significance. As no strong relation was shown this result suggests that HLA-DRB3* could influence, but not completely determine, susceptibility to periodontitis and JIA. Whereas the positive association of HLA-B*27 and HLA-DRB1*11 to JIA and the negative association of HLA-DRB1*07 yielded in the present study were confirmed by another German study (Minden et al. 2001), an association between JIA and HLA-DRB3* has not been reported so far. The supertype HLA-DRB3*(DR52) was found to be positively associated to the primary Sjorgren syndrome (Wang et al. 1997), a chronic autoimmune disease, that was found related to female gender (Alamano et al. 2006), arthritis (Ramos-Casals et al. 2006), and chronic periodontitis (Najera et al. 1997). These results

Table 5. Backward stepwise binary logistic regression in order to determine the individual odds ratio of HLA-A*01 (model 1) and HLA-A*01:DRB3* (model 2) for periodontitis in the JIA group with respect to the cofactors age, gender, smoking, duration of the JIA disease, and API

Significant variables	Regression coefficient	SE	p-values	Odds Ratio	95% CI	
					lower	upper
<i>Model 1</i>						
API	0.031	0.011	0.005	1.032	1.01	1.06
HLA-A*01	1.517	0.617	0.014	4.599	1.36	15.26
<i>Model 2</i>						
API	0.030	0.011	0.009	1.030	1.01	1.05
HLA-A*01:DRB3*	1.465	0.680	0.031	4.329	1.14	16.4

SE, standard error; CI, confidence interval; API, approximal plaque; HLA, human leucocyte antigen; JIA, Juvenile idiopathic arthritis.

confirmed the relationship between HLA-DRB3* and female gender and the role of HLA-DRB3* as a risk indicator for JIA and periodontitis revealed in the present study.

The revealed gender-specific HLA associations in periodontitis (for instance, no HLA associations among periodontitis males) could be caused by a relationship between the serum level of sex hormones and the HLA phenotype (Gerencer et al. 1982). Gender-specific HLA associations were also shown for rheumatic diseases such as Reiter's disease, ankylosing spondylitis, acute anterior uveitis, and psoriatic arthritis (James 1991), for leukaemia (Dorak et al. 1995), and mixed forms of psoriasis vulgaris and atopic dermatitis (Stepanova et al. 2004).

It is striking that HLA-DRB3* occurred more frequently in the group of JIA patients among subjects with periodontitis than among individuals without periodontitis (Table 4). Despite the fact that the JIA group with periodontitis had a higher percentage of patients with polyarthritis owing to a more restricted oral hygiene the combination HLA-DRB3*:HLA-A*01 and the single allele HLA-A*01 represent plaque independent risk indicators for attachment loss (Table 5 models 1 and 2). The associations between HLA-DRB3*:A*01 and CAL and HLA-A*01 and CAL can be explain by the following mechanisms.

Firstly, it has been shown that the recognition and binding of bacterial peptides can be influenced by HLA-DRB3*(DR52) genetic variants. In the hypervariable DR β region of the latter a dimorphism at position 86 (glycine/valine) like in HLA-DRB1*01, -DRB1*11, and -DRB1*13, has been reported that affects allrecognition and antigen presentation (Verreck et al.

1996). Interestingly, in the present study HLA-DRB1*11 was increased in JIA-patients (Table 1) whereas HLA-DRB1*13 occurred more frequently in patients with AP (Table 2). These findings underline the importance of certain HLA-DR alleles for JIA (DRB1*11), periodontitis (DRB1*13), or both diseases (DRB3*).

Secondly, mimicry of periodontopathic peptides to HLA could lead to autoimmune reactions or cross tolerance. Furthermore, the formation of specific autoantibodies (SSA, SSB) is caused by the supertype HLA-DRB3*(DR52). This has been shown, for instance, for the primary Sjogren syndrome (Wang et al. 1997). Moreover, certain natural peptides recognized by HLA-DRB3* determined DR52 molecules carry the same peptide motif (KDYLALNEDLRSWTAADT) as HLA-A1 (Verreck et al. 1996). For this HLA-A1 motif we uncovered in the databank Fasta [URL <http://www.ebi.ac.uk/fasta33/genomes.html> (accessed on 23 August 2006)] sequence homologous peptides of *Porphyromonas gingivalis* with sequence identities ranging from 60% to 36%. Among them we found the immunoreactive 61 kDa antigen PG91 (UNIPROT:Q9S3R0, Nelson et al. 2003). By this mechanism, the same immunodominant determinants of periodontopathic bacteria and HLA-A*01 may be able to induce cross-reactive autoantibodies that are included in the pathway of JIA.

In the present study it was shown that HLA-B*35, HLA-A*01:B*35, and HLA-B*27 occurred with increased frequency in the JIA group with CAL, whereas HLA-A*24 was decreased (Table 4). However, there was no significance considering age, gender, smoking, and API. Therefore, these HLA markers are not plaque level

independent risk or resistant indicators for CAL within JIA patients. However, under animal-experimental conditions another study confirmed the relationship between CAL and HLA-B*27. For HLA-B27 transgenic rats, strong immunoreactivity against periodontitis bacteria and an accelerated alveolar bone loss was shown in comparison with wild-type rats (Tatakis et al. 2002).

To sum up, HLA-DRB3* was positively associated with both females suffering from JIA and females suffering from CP. Moreover, the expression of HLA-DRB3* together with HLA-A*01 increased the OR for periodontitis in the JIA group considering established cofounders for periodontitis. Hence, HLA-DRB3* is a putative risk indicator for JIA and chronic periodontitis among females.

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Clinical Relevance

Scientific rationale for the study: The aetiology of both periodontitis and JIA could be influenced by factors inherent in the HLA system. The aim was to examine the problem of whether there are common HLA markers in JIA and periodontitis.

Principal findings: Among females the expression of HLA-DRB3* was positively associated with JIA and CP. HLA-A*01 and HLA-A*01:DRB3*(DR52) increased the risk for attachment loss in the JIA group considering established confounding variables for periodontitis.

Practical implications: JIA patients who express HLA-A*01 or HLA-A*01:DRB3*(DR52) should be checked with respect to early attachment loss at regular intervals.