Human leukocyte antigen polymorphism in chronic and aggressive periodontitis among Caucasians: a meta-analysis

Jamal M. Stein[1], Helmut K. G. Machulla[3], Ralf Smeets[4], Friedrich Lampert[1] and Stefan Reichert[2]

[1]Department of Operative Dentistry, Periodontology and Preventive Dentistry, University Hospital (RWTH), Aachen, Germany; [2]Department of Operative Dentistry and Periodontology, University School of Dental Medicine; [3]Interbranch HLA Laboratory, Department GHATT, Institute of Medical Immunology, Martin-Luther University, Halle-Wittenberg, Germany; [4]Department of Oral and Maxillofacial Surgery, University Hospital (RWTH), Aachen, Germany

Abstract

Aim: Multiple studies have reported associations between periodontitis and particular human leukocyte antigens (HLA). Because associations are inconsistent, we conducted a systematic literature review and a meta-analysis focusing on Caucasian case–control studies.

Material and Methods: A literature search reporting on the distribution of HLA class I and II phenotypes in Caucasian patients with chronic periodontitis (CP) and aggressive periodontitis (AP) was performed. Data sources included electronic databases and bibliographies of published articles. Screening and data abstraction were conducted independently by different reviewers.

Results: Out of 174 publications, 12 studies were considered to be suitable for meta-analysis. In patients with CP, no significant HLA associations were found. Patients with AP showed a positive association with HLA-A9 [odds ratio = 2.59 (95% confidence interval 1.36–4.83), $p = 0.004$] and HLA-B15 [1.90 (1.15–3.16), $p = 0.01$] as well as a negative association with HLA-A2 [0.72 (0.56–0.94), $p = 0.01$] and -B5 [0.49 (0.30–0.79), $p = 0.004$]. On grouping all patients into one periodontitis group (AP+CP), the same deviations were confirmed with higher statistical significance. For HLA-A9 and -B15, significant heterogeneity was found between the studies. No significant associations were found with HLA class II antigens.

Conclusions: HLA-A9 and -B15 seem to represent susceptibility factors for AP whereas HLA-A2 and -B5 are potential protective factors against periodontitis among Caucasians.

Tissues of the oral cavity represent one of the most important gates for pathogens to enter the host organism, with the potential to develop infectious diseases. Teeth surrounding gingival sulcus offer microorganisms a unique pathway to form matrix-enclosed biofilms (Socransky & Haffajee 2002) that can be colonized by at least 500 bacterial taxa (Paster et al. 2001). As a consequence, bacterially induced inflammation of the gingiva (gingivitis) occurs with a prevalence of 80–100% in children, young adults and adolescents (Hugoson et al. 1981, Cutress 1986, Jenkins & Papapanou 2001). Gingival inflammation can be self-limited with little or no discernible clinical consequences. Depending on the local ecological conditions of the gingival sulcus and host response, periodontopathic bacteria of the biofilm are able to overgrow opportunistically (Socransky & Haffajee 1992) and are considered to be factors promoting destructive periodontitis resulting in irreversible loss of both the connective tissue and the bony attachment. However, despite the high prevalence of individuals harbouring bacterial pathogens, only a limited group of otherwise healthy individuals exhibit rapidly progressing severe aggressive periodontitis (AP) while others have no or only

slowly progressing moderate (chronic) forms of periodontal disease. Thus, microbial factors alone are not able to explain interindividual differences in the outcome and course of periodontal diseases.

Susceptibility to periodontal disease has been convincingly demonstrated to be determined in part by genetic predisposition (Hart & Kornman 1997, Michalowicz et al. 2000). Recognition of antigen peptides and their presentation to T cells is crucial for an effective antigen-specific immune response towards periodontal pathogens and underlies genetic control. Because antigen presentation to and thereby activation of T cells is restricted by the major histocompatibility complex (MHC), the polymorphism of the human MHC molecules [human leukocyte antigens (HLA)] can directly affect the binding capability of antigen peptides and thus the antigen-specific T-cell response (Zinkernagel & Doherty 1997). Hence, this polymorphism could provide important susceptibility or resistance factors for periodontitis. Since the 1970s, several research groups have reported associations of HLA class I and II antigens with periodontal diseases. However, consistent results could not be obtained up to now because the studies varied in (i) terms of the number of HLA antigens investigated, (ii) the selection criteria of patients and controls as well as (iii) their ethnic origin. Furthermore, in many studies, (iv) only small numbers of patients ($N < 40$) were investigated. In most articles on HLA associations with chronic (CP) and (AP) forms of periodontitis, Caucasians were recruited. The heterogeneity of these studies makes it difficult to interpret their results, and longitudinal studies on HLA association have not been performed as yet. Therefore, the aim of this work was to undertake a systematic review of all relevant studies on HLA associations with CP and AP among Caucasians and to estimate the overall associations between HLA phenotypes by meta-analysis.

Material and Methods
Search strategy and selection criteria

All case–control studies that examined the frequency of HLA-A, -B, -Cw, -DR and/or -DQ phenotypes in Caucasians with aggressive or CP were eligible for this review. A literature search was

performed on electronic databases MEDLINE (1966–2007) and EMBASE (1988–2007). Only papers written in English were considered. Furthermore, the reference lists of all the studies and review articles published in English were screened for additional publications.

For the primary search in both databases, a combination of disease population terms and outcome terms was applied:

Disease population terms:

- MeSH terms (MEDLINE): ''Periodontal diseases'' OR
- Headings/all subheadings (EMBASE): ''Periodontal disease'' OR
- Text words: ''Periodontal diseases'' OR ''Periodontitis'' OR ''Periodontosis'' OR ''Juvenile Periodontitis'' OR ''Adult Periodontitis'' OR ''CP'' OR ''Aggressive Periodontitis'' OR ''Rapidly Progressive Periodontitis'' OR ''Early-Onset Periodontitis''

Outcome terms:

- MeSH terms (MEDLINE): ''MHC'' OR ''HLA Antigens'' OR
- Headings/all subheadings (EMBASE): ''MHC'' OR ''HLA Antigen'' OR
- Text words: ''MHC Genes'' OR ''human leukocyte antigens'' OR ''HLA Antigens''

Combined terms:

- Disease population and outcome terms

A diagnosis of AP was accepted if the diagnostic criteria were in accordance with those of the latest nomenclature of the American Academy of Periodontology (AAP) (Armitage 1999) or correlated to the criteria provided by Tonetti & Mombelli (1999) for ''localized juvenile periodontitis (LJP)'' and ''generalized early-onset periodontitis (G-EOP)''. In terms of defining CP, both the terms ''chronic'' and ''adult'' periodontitis were accepted if the diagnostic criteria met those of CP provided by the latest nomenclature of the AAP (Armitage 1999). Studies on CP compared with controls with unknown periodontal status were excluded because the control group can be expected to include a high number of subjects with CP due to the high prevalence of CP (18–81% among subjects older than 35 years of age) (Flemmig 1999). In studies on AP, controls with unknown periodontal

status were accepted as the chance of finding patients with AP among controls was very low and considered to be statistically negligible due to the low incidence of AP (ranging from 0.1% for localized to 3.6% for generalized forms) (Loe & Brown 1991, Papapanou 1996).

Two reviewers (J. S. and S. R.) independently screened the titles and abstracts of the search results for possible inclusion in the review. After exclusion of publications on studies other than case–control ones, the full text of all the remaining papers was then obtained for independent assessment against the stated inclusion criteria by three reviewers (J. S., S. R. and H. M.). Any disagreements were resolved by consensus. Because meta-analysis required the knowledge of HLA phenotype frequencies, studies with inappropriate data presentation or inconsistent calculation of HLA phenotype frequencies and/or its statistical significance were excluded. This was also the case if the results of a study have been included in more recent papers. When necessary, authors were contacted for additional information. Table 1 shows the criteria for inclusion and exclusion of the relevant studies.

Studies using either serological or polymerase chain reaction (PCR) techniques to identify HLA type were considered for this review. Moreover, both studies reporting HLA phenotype frequencies of HLA main determinants (e.g. HLA-A9) and HLA split antigens, e.g. HLA-A23 and -A24 (split antigens of HLA-A9), were included. Meta-analysis was not performed on any allele that was identified in only one study.

Quantitative data analysis

The overall odds ratios (OR) and 95% confidence intervals (CI) were calculated for all published HLA phenotypes using the Review Manager version 4.2 software (Update Software Ltd., Oxford, UK). Statistical heterogeneity was calculated with the χ^2 test. HLA phenotypes with evidence of homogeneity ($p > 0.10$) were further analysed with a fixed-effects model (Mantel & Haenszel 1959); those with heterogeneous effects ($p \leqslant 0.10$) were further studied with a random-effects model (DerSimonian & Laird 1986). The fixed-effect method provides an estimate of an overall OR and variance for an allele, when the variation of the estimates is assumed to

Table 1. Criteria for in- and exclusion of studies on HLA associations with chronic (CP) and aggressive (AP) periodontitis for systematic review and meta-analysis

Criteria	Studies on HLA associations with CP		Studies on HLA associations with AP	
	inclusion	exclusion	inclusion	exclusion
Type of study	Case–control	Other than case–control	Case–control	Other than case–control
Ethnic origin of study populations	Caucasians	No Caucasians, mixed or unknown	Caucasians	No Caucasians, mixed or unknown
Patients	Defined according to the criteria for ''chronic'' or ''adult periodontitis''	Cannot be referred to the criteria for ''chronic'' or ''adult periodontitis''	Defined according to the criteria for ''aggressive'', ''early-onset'', ''rapidly progressive'' ''localized'' or ''generalized juvenile periodontitis''	Cannot be referred to the criteria for ''aggressive'', ''early-onset (EOP)'', ''rapidly progressive'' (RPP), ''localized/ generalized (LJP/GJP) juvenile periodontitis (JP)''
Controls	Defined as periodontitis free	Not defined as periodontitis free	Periodontitis free or not examined	–
Data presentation (HLA phenotype frequencies, calculation of statistical significance)	Consistent and reproducible	Inconsistent and/or not reproducible	Consistent and reproducible	Inconsistent and/or not reproducible
Subjects included in recent HLA association papers	No	Yes	No	Yes

HLA, human leukocyte antigens.

be as a result of random sampling error. The random-effects model considers variation across studies as well as variation of the allelic effect (within-study variation).

Results

Search results and study characteristics

The primary search resulted in the identification of 174 publications on HLA and periodontitis using the stated search criteria, out of which 28 case–control studies on HLA association with chronic and AP could be selected. Of these studies, 19 dealt with probands of Caucasian origin. According to the inclusion criteria, 12 publications were considered to be suitable for meta-analysis (Fig. 1), while seven studies were excluded because of results published in recent HLA association studies and inappropriate data presentation (Table 2). Out of the included studies, nine reported HLA associations in patients with AP (Table 3), and six in patients with CP (Table 4).

Reinholdt et al. (1977) examined both patients with adult (chronic) and juvenile (aggressive) periodontitis, out of which only patients with juvenile periodontitis were included in the meta-analysis. The patient group with adult periodontitis was excluded because the control group was not free from periodontitis.
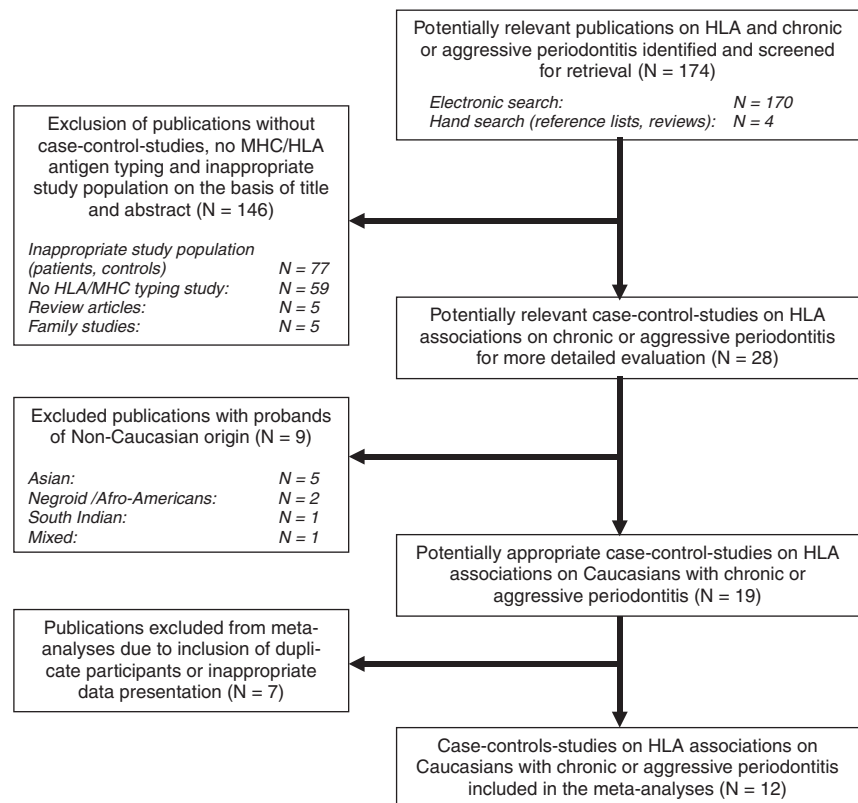

Fig. 1. Flow diagram for inclusion of studies in the meta-analysis.

The results of the study of Terasaki et al. (1975) have also been published in the study by Kaslick et al. (1975) and, moreover, were included in the follow-up study of Kaslick et al. (1980), except for the results of HLA-B5 and -B18 (Dr. R. Kaslick, personal communication). Therefore, only for the phenotype frequencies of HLA-B5 and -B18 was the study of Terasaki et al. (1975)

Table 2. Excluded case–control studies on HLA associations on Caucasians with chronic (CP) and aggressive periodontitis (AP) excluded from systematic review

Author (year)	Patients (N)	Controls (N)	Reported HLA associations	Reason for exclusion
Kaslick et al. (1975)	JP (19) AdultP (28)	No period. (41)	JP: A2 ↓ AdultP: A2 ↓	Results already published in *Terasaki et al. (1975)* and also included in the follow-up study by *Kaslick et al. (1980)*
Marggraf et al. (1983)	ProfP (50)	BD (257)	A9 ↑, B44 ↑, B35 ↑, Cw4 ↑	Diagnosis could not be referred to chronic or aggressive periodontitis; discrepancies in calculation of phenotype frequencies (e.g. pf [HLA-B12+] > pf [HLA-B44+])
Topic et al. (1986)	LJP (40)	Popul. (1000)	A1 ↑, A2 ↑, A3 ↑, B35 ↑ B12 ↑, B18 ↑, B40 ↑	Discrepancies in calculation of HLA phenotype frequencies and statistical significance as basis for interpretation
Firatli et al. (1996)	JP (30) RPP (30)	Popul. (3731)	JP+RPP: A9 ↑, DR4 ↑, A1 ↓, A2 ↓	Discrepancies in calculation of HLA phenotype frequencies and/or calculation of statistical significance as basis for interpretation
Dyer et al. (1997)	AdultP (15)	No period. (15)	DR4 ↑, DR53 ↑, DQ3 ↑	Results have already been published in *Alley et al. (1993)*
Reichert et al. (2003)	AP (50) CP (102)	No period. (102)	Variety of associations	Differentiation of the results of Machulla et al. (2002) as to gender differences in HLA association (original data published in Machulla et al. 2002)
Stein et al. (2003)	AP (50) CP (102)	No period. (102)	Variety of associations	Differentiation of the results of Machulla et al. (2002) as to HLA allele combinations (original data published in Machulla et al. 2002)

AdultP, adult periodontitis; CP, chronic periodontitis; AP, aggressive periodontitis; JP, juvenile periodontitis; LJP, localized juvenile periodontitis; RPP, rapidly progressive periodontitis, ProfP, profound periodontitis; BD, blood doners; popul., population; no period., no periodontitis; HLA, human leukocyte antigens.

Table 3. Case-control studies on HLA associations on Caucasians with aggressive periodontitis (AP) included in meta-analysis

Authors	Year	Population	Patients (N)	Controls (N)	Reported HLA associations
Terasaki et al.[*]	1975	USA	JP (19)	No periodontitis (41)	A2 ↓
Reinholdt et al.	1977	Denmark	JP (39)	Population (1967)	A9 ↑, A28 ↑, B15 ↑
Kaslick et al.	1980	USA	JP (33)	No periodontitis (53)	A2 ↓
Cullinan et al.	1980	England	JP (12)	Population (174)	A30 ↓, B12 ↓
Klouda et al.	1986	England	RPP (44)	Cadaver kidney donors (2041)	A9 ↑ (A24 ↑)
Katz et al.	1987	Israel	RPP (10)	Blood donors (120)	DR4 ↑
Amer et al.	1988	England	RPP (49)	No periodontitis (40)	A10 ↓
Shapira et al.	1994	Israel	LJP (11)	Unexamined volunteers (113)	–
			SGP (15)	Unexamined volunteers (113)	A9 ↑ (A24 ↑), B15 ↑
Machulla et al.	2002	Germany	RPP (50)	No periodontitis (102)	A11 ↑, A29 ↑, DRB1*13 ↑, A31 ↓, A30/31 ↓, DRBbl ↓

The arrows show whether a marker was found more (↑) or less (↓) frequent among patients. DRBbl, DRBblank (no DRB3/4/5).
[*]Terasaki et al. (1975) was only included for calculation of HLA-B18 and HLA-B5, all other results included in Kaslick et al. (1980).
JP, juvenile periodontitis, RPP, rapidly progressive periodontitis, LJP, localized juvenile periodontitis, SGP, severe generalized periodontitis; HLA, human leukocyte antigens.

Table 4. Case–control studies on HLA associations on Caucasians with chronic periodontitis (CP) included in meta-analysis

Authors	Year	Population	Patients (N)	Controls (N)	Reported HLA associations
Terasaki et al.[*]	1975	USA	Adult P (28)	No periodontitis (41)	A2 ↓
Kaslick et al.	1980	USA	Adult P (41)	No periodontitis (53)	A2 ↓
Goteiner & Goldman	1984	USA	Adult P (15)	No periodontitis (15)	B5 ↓
Blandin-Texier et al.	1986	France	CP (62)	No periodontitis (44)	A9 ↑
Alley et al.	1993	USA	Adult P (15)	No periodontitis (15)	DR4 ↑
Machulla et al.	2002	Germany	Adult P (102)	No periodontitis (102)	A11 ↑, A29 ↑, B14 ↑, Cw8 ↑, A3 ↓, A31 ↓, A30/31 ↓

Adult P, adult periodontitis, CP, chronic periodontitis; HLA, human leukocyte antigens. The arrows show whether a marker was found more (↑) or less (↓) frequent among patients.
[*]Terasaki et al. (1975) was only included for calculation of HLA-B18 and HLA-B5, all other results included in Kaslick et al. (1980).

Table 5. HLA-antigens included in meta-analysis for chronic (CP) and aggressive (AP) periodontitis

Studies with	HLA-A	HLA-B	HLA-Cw	HLA-DR	HLA-DQ
CP	A1, A2, A3, A9, A10, A11, A29 (A19), A28	B15, B18, B5	–	DR1, DR2, DR3, DR4, DR5, DR6, DR7, DR8, DR9, DR10	DQ1, DQ6 (DQ1), DQ2, DQ3
AP	A1, A2, A3, A9, A23 (A9), A24 (A9), A10, A11, A29 (A19), A30 (A19), A31 (A19), A28	B51 (B5), B52 (B5), B12, B44 (B12), B45 (B12), B13, B14, B15, B18, B27, B35, B40	Cw1, Cw2, Cw3, Cw4, Cw5, Cw6, Cw7, Cw8	DR1, DR2, DR3, DR4, DR5, DR6, DR7, DR8, DR9, DR10	–

HLA, human leukocyte antigens.

considered for meta-analysis, for all other HLA antigens, the follow-up study of Kaslick et al. (1980) was included. The paper of Kaslick et al. (1975) was excluded (Table 2).

In the publications of Cullinan et al. (1980) and Goteiner & Goldman (1984), both Caucasian and Negroid patient and control groups have been reported. For meta-analysis, only the Caucasian groups of patients and controls have been considered.

MHC and CP

Given at least two studies for each examined HLA marker, it was possible to perform a meta-analysis for 25 HLA markers (11 HLA class I, 14 HLA class II markers; Table 5) in patients with CP. Combined analysis of all HLA antigen frequencies did not reveal any significant positive or negative associations. There was only a slight tendency for an increased frequency of HLA-A9, -B15 and -A29 (A19) and a decreased occurrence of HLA-A2, A3 and -B5 among patients with CP (Table 6).

MHC and AP

In patients with AP, meta-analysis was performed for 42 HLA markers (32 HLA class I, 10 HLA class II markers; Table 5). Calculations resulted in significantly positive associations of HLA-A9 and -B15 with increased OR, whereas HLA-A2 and -B5 had significantly negative associations with lower frequencies of these markers among the patients (Table 6). Interestingly, the HLA associations of HLA-A2 and -B5 showed homogenous effects between all studies. There are not enough data to demonstrate whether the associations of HLA-A9, -B15 and -B5 were caused by the association of only one or both their split antigens (HLA-A23, -A24 for HLA- A9; HLA-B62, -B63, -B75, -B76, -B77 for HLA-B15; and HLA-

B51, -B52 for HLA-B5). However, among those studies that considered the split antigens, association with HLA-A9 was mainly caused by HLA-A24 (five studies: phenotype frequency = 27.37% *versus* 17.01%; OR = 2.01; $p = 0.12$). Only two studies (Shapira et al. 1994, Machulla et al. 2002) examined HLA-B15 split antigens, but none of the splits showed a predominant association. Besides, there was a slight non-

significant trend for a lower frequency of HLA-DR1 in AP patients (Table 6).

MHC and periodontitis (CP+AP)

In order to increase the power of the study, both groups with AP and CP were grouped into one periodontitis group. This patient group can be considered to consist of patients with periodontitis independent of the age of onset. In this

Review: HLA associations to periodontal disease among Caucasians (Version 01)
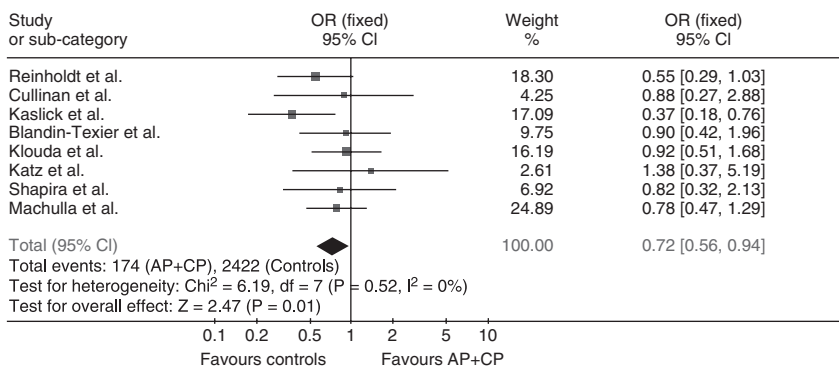Comparison: 04 AP+CP versus controls
Outcome: 01 HLA-A2

Fig. 2. Combined analysis of the odds ratio (OR) of HLA-A2 in patients with periodontitis (AP+CP). AP, aggressive periodontitis; CP, chronic periodontitis.

Review: HLA associations to periodontal disease among Caucasians (Version 01)
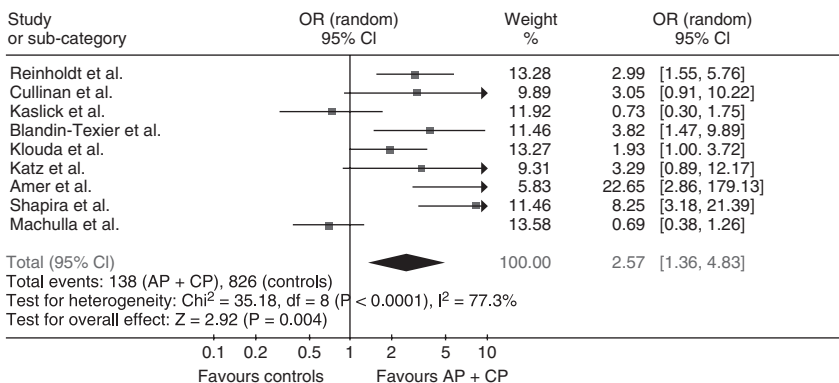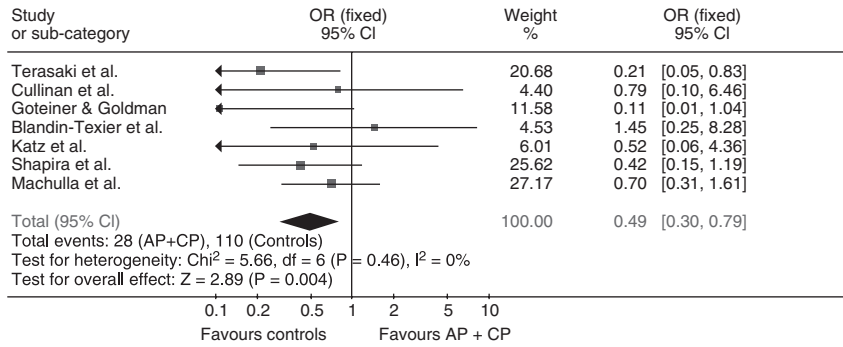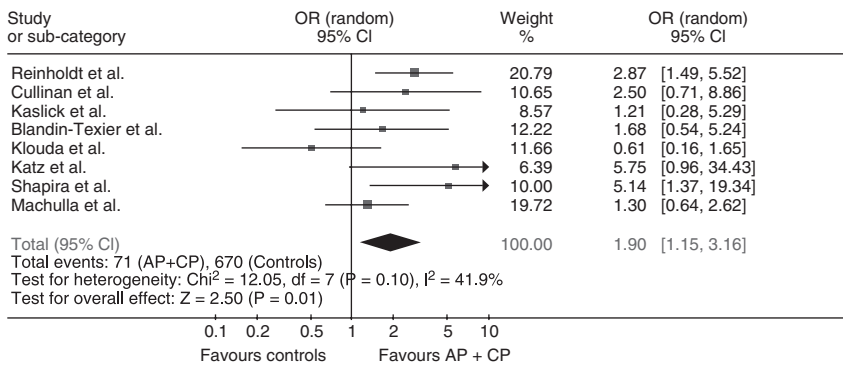Comparison: 04 AP+CP versus controls
Outcome: 03 HLA-A9

Fig. 3. Combined analysis of the odds ratio (OR) of HLA-A9 in patients with periodontitis (AP+CP). AP, aggressive periodontitis; CP, chronic periodontitis.

Review: HLA associations to periodontal disease among Caucasians (Version 01)
Comparison: 04 AP+CP versus controls
Outcome: 02 HLA-B5

Study or sub-category	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Terasaki et al.		20.68	0.21 [0.05, 0.83]
Cullinan et al.		4.40	0.79 [0.10, 6.46]
Goteiner & Goldman		11.58	0.11 [0.01, 1.04]
Blandin-Texier et al.		4.53	1.45 [0.25, 8.28]
Katz et al.		6.01	0.52 [0.06, 4.36]
Shapira et al.		25.62	0.42 [0.15, 1.19]
Machulla et al.		27.17	0.70 [0.31, 1.61]
Total (95% CI)		100.00	0.49 [0.30, 0.79]

Total events: 28 (AP+CP), 110 (Controls)
Test for heterogeneity: Chi² = 5.66, df = 6 (P = 0.46), I² = 0%
Test for overall effect: Z = 2.89 (P = 0.004)

0.1 0.2 0.5 1 2 5 10
Favours controls   Favours AP + CP

Fig. 4. Combined analysis of the odds ratio (OR) of HLA-B5 in patients with periodontitis (AP+CP). AP, aggressive periodontitis; CP, chronic periodontitis.

Review: HLA associations to periodontal disease among Caucasians (Version 01)
Comparison: 04 AP+CP versus controls
Outcome: 04 HLA-B15

Study or sub-category	OR (random) 95% CI	Weight %	OR (random) 95% CI
Reinholdt et al.		20.79	2.87 [1.49, 5.52]
Cullinan et al.		10.65	2.50 [0.71, 8.86]
Kaslick et al.		8.57	1.21 [0.28, 5.29]
Blandin-Texier et al.		12.22	1.68 [0.54, 5.24]
Klouda et al.		11.66	0.61 [0.16, 1.65]
Katz et al.		6.39	5.75 [0.96, 34.43]
Shapira et al.		10.00	5.14 [1.37, 19.34]
Machulla et al.		19.72	1.30 [0.64, 2.62]
Total (95% CI)		100.00	1.90 [1.15, 3.16]

Total events: 71 (AP+CP), 670 (Controls)
Test for heterogeneity: Chi² = 12.05, df = 7 (P = 0.10), I² = 41.9%
Test for overall effect: Z = 2.50 (P = 0.01)

0.1 0.2 0.5 1 2 5 10
Favours controls   Favours AP + CP

Fig. 5. Combined analysis of the odds ratio (OR) of HLA-B15 in patients with periodontitis (CP+AP). AP, aggressive periodontitis; CP, chronic periodontitis.

analysis, the negative associations to HLA-A2, -B5 and the positive associations with HLA-A9 and -B15 found in the AP group could be confirmed for all periodontitis patients (Table 6) (Figs 2–5). The associations with HLA-A9 and -B5 showed the highest value of statistical significance.

Discussion

Two of the main problems in defining genetic risk factors for periodontitis are the heterogeneity of the examined diseases and ethnic aspects of the distribution of the genetic markers. In the systematic review presented, which is the first on this topic, only studies on Caucasians were included because most information about HLA and periodontitis is available in these populations and thus was felt to be suitable for a first combined analysis. Similarly, we focused on case–control studies as the majority of published articles reported this type of study, which is again suitable for meta-analysis, whereas no cohort study and only a few segregation analyses in families are available.

A search strategy was chosen that only allowed the inclusion of articles, in which patient groups were clearly defined according to the criteria of the latest nomenclature and controls were

Table 6. Deviations of HLA-antigen frequencies in patients with chronic periodontitis (CP), aggressive periodontitis (AP) and total group of aggressive and chronic periodontitis (AP+CP) in comparison to control probands

HLA	Studies	Patients (n/pf)	Controls (n/pf)	Heterogeneity (p)	Model	OR*	Overall effect (p)	95% CI
CP								
A2	D, F, K	90/43.90	103/51.76	0.53	Fixed	0.72	>0.05	0.49, 1.07
A3	F, K	36/21.95	44/30.14	0.20	Fixed	0.65	>0.05	0.39, 1.09
A9	D, F, K	56/27.32	45/22.61	0.02	Random	1.36	>0.05	0.51, 3.60
A29 (A19)	F, K	14/8.54	5/3.42	0.15	Fixed	2.40	>0.05	0.85, 6.83
B5	A, E, F, K	15/7.25	30/14.85	0.08	Random	0.42	>0.05	0.11, 1.61
B15	D, F, K	31/15.12	22/11.06	0.83	Fixed	1.37	>0.05	0.76, 2.48
AP								
A2	B, C, D, G, H, J, K	84/39.25	2401/52.54	0.59	Fixed	**0.69**	**0.01**	0.51, 0.93
A9	B, C, D, G, H, I, J, K	82/31.18	819/17.77	0.0001	Random	**2.39**	**0.02**	1.16, 4.92
B5	A, C, H, J, K	13/11.11	102/18.55	0.99	Random	**0.50**	**0.03**	0.26, 0.95
B15	B, C, D, G, H, J, K	40/18.69	665/14.55	0.08	Random	**2.03**	**0.02**	1.11, 3.72
DR1	H, J, K	9/10.47	55/16.42	0.85	Fixed	0.49	>0.05	0.22, 1.05
Total periodontitis group (CP+AP)								
A2	B, C, D, F, G, H, J, K	174/41.53	2422/52.49	0.52	Fixed	**0.72**	**0.01**	0.56, 0.94
A9	B, C, D, F, G, H, I, J, K	138/29.49	826/17.75	< 0.0001	Random	**2.57**	**0.004**	1.36, 4.83
B5	A, C, E, F, H, J, K	28/8.64	110/18.06	0.46	Fixed	**0.49**	**0.004**	0.30, 0.79
B15	B, C, D, F, G, H, J, K	71/16.95	670/14.52	0.01	Random	**1.90**	**0.01**	1.15, 3.16

*Unadjusted for any confounders.

pf, phenotype frequency; HLA, human leucocyte antigens; OR, odds ratio ; CI, confidence interval; fixed, fixed effects-model; random, random-effects model; A–I refer to the following studies: A, Terasaki et al. (1975); B, Reinholdt et al. (1977); C, Cullinan et al. (1980); D, Kaslick et al. (1980); E, Goteiner & Goldman (1984); F, Blandin-Texier et al. (1986); G, Klouda et al. (1986); H, Katz et al. (1987); I, Amer et al. (1988); J, Shapira et al. (1994); K, Machulla et al. (2002).

of CTL, e.g. HLA-A2 restricted CTL response towards EBV/HCMV peptides of the lytic phase (EBV-derived Rta; HCMV-derived IE (Frankenberg et al. 2002, Khan et al. 2002) or HLA-A2 and -B5 restricted CTL response against EBV/HCMV peptides of the latent phase [EBV-derived EBNA (Burrows et al. 1994, Lee et al. 1997, Pepperl et al. 1998)], LMP (Steven et al. 1997, Khanna et al. 1999); HCMV-derived pp65 (Wills et al. 1996), which could prevent infection of immunocompetent cells by and/or limit reactivation of herpes-viruses so that an immune response against periodontopathic bacteria can be perpetuated.

Strength and limitations of the study

Our study has several strengths. Owing to combined analysis, it was possible to compare a large number of patients with AP and CP with their controls, reaching a higher statistical power than the pre-viously published articles. Owing to selection of studies in which study populations belong to the same ethnic origin and controls were free of the corresponding disease, publication bias could be reduced and a high contrast between diseased and healthy subjects could be achieved. Finally, due to meta-analysis all previously reported HLA associations with periodontitis among Caucasians have been limited to only four potentially relevant HLA antigens.

The present study also has potential limitations that have to be considered. First, the results of this paper are only applicable to Caucasian populations. Because the results of studies on Blacks (Cogen et al. 1986, Moses et al. 1994) and Japanese (Ashikaga 1984, Ohyama et al. 1996) suggest that alleles other than those shown in the review may be associated with AP or CP, a separate review is recommended for other non-Caucasian populations. Second, although a comprehensive data search has been carried out, a few studies might not have been identified if they were not listed in databases or reference lists or they were not considered for publication because of reporting no or only a few HLA associations (publication bias). Further-more, we only focused on HLA main and split antigens, not on alleles. However, we think that identification of associated HLA main antigen determi-nants must be the first step for a more detailed focus on HLA antigen alleles

providing the base for peptide-binding analyses.

In summary, we found a positive association of HLA-A9, -B15 and a negative association of HLA-A2 and -B5 for AP and a total periodontitis group (CP+AP). Based on the current knowledge about herpesviruses in periodontitis and epitope restriction by the associated HLA markers, we hypothe-size that HLA-A9- and -B15-positive patients might be at a higher risk of an inadequate (antiviral) immune response with an advanced (aggressive) course of periodontitis, while HLA-A2- and -B5-positive patients might be more capable of controlling viral–bacterial co-infection and thus preventing periodontitis.

It is recommended that, in future, multi-centre studies with well-defined study populations regarding known risk factors for periodontitis are carried out in order to verify and specify the presented associations, especially their benefit as potential prognostic markers. Further studies should also focus on the level of HLA alleles and their ability to bind herpesviral epitopes and stimulate effective CTL responses.

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Address:
Jamal M. Stein
Department of Operative Dentistry
University Hospital Aachen (RWTH)
Periodontology and Preventive Dentistry
Pauwelsstrasse 30, D-52074 Aachen
Germany
E-mail: JStein@ukaachen.de

Clinical Relevance

Scientific rationale for the study: HLA antigens have been considered to be genetic background factors for periodontitis. Owing to inconsistencies in the results of previous reports, a meta-analysis was performed on HLA case–control studies in Cauca-sians with chronic (CP) and aggres-sive (AP) periodontitis.

Principal findings: No significant asso-ciation with CP was found. HLA-A9 and -B15 were positively associated with AP. HLA-A2 and -B5 showed a negative association with AP and a total periodontitis group (CP+AP).

Practical implications: The results provide a focus for future studies to verify the diagnostic and prognostic value of HLA-A9, -B15 as potential risk markers for AP and HLA-A2, -B5 as protective factors efficiently controlling periodontal infection.