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HLA Associations to Periodontitis: a Meta-analysis

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Introduction

Susceptibility to periodontal disease (PD) has been convincingly demonstrated to be in part determined by genetic predisposition (1, 2). Due to their central role in immune response against periodontopathogenic bacteria HLA antigens have been the subject of several investigations. The high polymorphism of the HLA system results in differences of peptid binding capability and subsequently individual immune reaction and degree of responsiveness to antigenic peptids (Fig. 1). Several studies have shown certain HLA antigens to be associated with PD. The results of the more or less significantly associated HLA antigens are, however, not conclusive because the studies vary in terms of the number of investigated HLA antigens, the number and selection criteria of patients and controls as well as their ethnic origin.

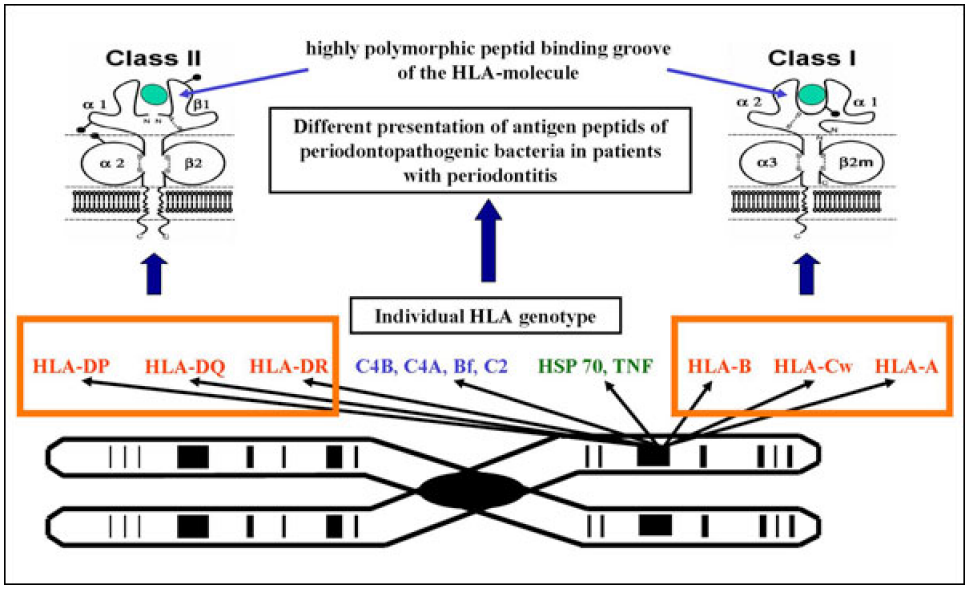

Fig 1: Organisation of HLA class I and II genes on chromosome 6 and HLA-dependent binding capability of antigen peptids

Objectives

Therefore, the aim of the presented study was to estimate the overall associations between HLA phenotypes among Caucasians and to establish the odds ratio conferred by HLA phenotypes by meta-analysis.

Material and Methods

All publications reporting HLA-A, -B, -Cw, -DR, and -DQ antigen frequency in Caucasian patients with periodontal disease compared with controls were identified by electronic search of Medline (1966-2004) using a combination of subject headings and text words relating to the terms "periodontal disease\", "periodontitis", "periodontosis", "chronic", "adult", "early-onset", "aggressive", "juvenile", "rapidly", "progressive", "HLA" and "MHC". In addition, reference lists of all articles selected for inclusion were screened. Periodontal diagnoses were adapted to the latest nomenclature of the AAP. Publications, in which diagnostic criteria and definition of controls were not clearly described, were excluded. Studies on chronic periodontitis compared to controls with unknown periodontal status, were excluded. In studies on aggressive periodontitis controls with unknown periodontal status were accepted as the low incidence of aggressive periodontitis in Caucasian population is statistically negligable.
Overall odds ratios and 95% confidence intervals were calculated for all published HLA phenotypes using the Review Manager version 3.1 software (Update Software Ltd., Oxford, UK). Statistical heterogeneity was calculated with Chi2 test. HLA phenotypes with evidence of homogeneity ($p > 0.10$) were further analysed with a fixed-effects model (3); those with heterogeneous effects ($p \leq 0.10$) were further studied with a random-effects model (4).

Results

According to the selection criteria out of 18 case control studies 12 were suitable for meta-analysis (Table 1). As a part of the results of Terasaki et al. (5) were included in the data of Kaslick et al. (7), only the non-included HLA antigen frequencies were taken for meta-analysis. Two studies (18, 19) were excluded because of not reproducible statistical calculation of the presented HLA antigen frequencies.

Autor	Year	Population	Patient Group (N)	Control Group (N)	Associated HLA antigens
Terasaki et al.	1975	USA	JP (19)	no periodontitis (41)	↓ A2
			Adult P (28)	no periodontitis (41)	↓ A2
Reinholdt et al.	1977	Denmark	JP (39)	population (1967)	↑ A9, A28, B15
Kaslick et al.	1980	USA	JP (42)	no periodontitis (53)	↓ A2
			Adult P (41)	no periodontitis (53)	↓ A2
Cullinan et al.	1980	England	JP (12)	population (174)	↓ A30, B12
Goteiner & Goldman	1984	USA	Adult P (15)	no periodontitis (15)	↓ B5
Blandin-Texier et al.	1986	France	Chronic P (62)	no periodontitis (44)	↑ A9
Klouda et al.	1986	England	Rpp (44)	cadaver kidney doners (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
Alley et al.	1993	USA	Adult P (15)	no periodontitis (15)	↑ DR4
Shapira et al.	1994	Israel	L-EOP (11)	unexamined volunteers (113)	-
			G-EOP (15)	unexamined volunteers (113)	↑ A9, A24, B15
Machulla et al.	2002	Germany	Adult P (102)	no periodontitis (102)	↑ A11, A29, B14, Cw8 ↓ A3, A31, A30/31
			RPP (50)	no periodontitis (102)	↑ A11, A29, DR13 ↓ A31, A30/31, DRBblank

Tab 1: Studies on HLA associations in different forms of periodontal disease included in the meta-analysis. The arrows show whether a marker was found more or less frequent among patients.

Meta-analysis of all HLA antigen frequencies in chronic periodontitis revealed no positive associations, however HLA-A2 turned out to have a significantly negative association with a decreased odds ratio (Table 2 & Fig. 2). In the group of patients with aggressive periodontitis meta-analysis resulted in significantly positive associations of HLA-A9 and -B15 with increased odds ratios, whereas HLA-A2 and -B5 had significantly negative associations with lower frequencies of these markers among the patients (Table 3 & Fig. 3 - 6). Interestingly, the HLA associations of HLA-A2 and -B5 in aggressive perio-dontitis showed homogenous effects between all studies (Fig. 3, 5).

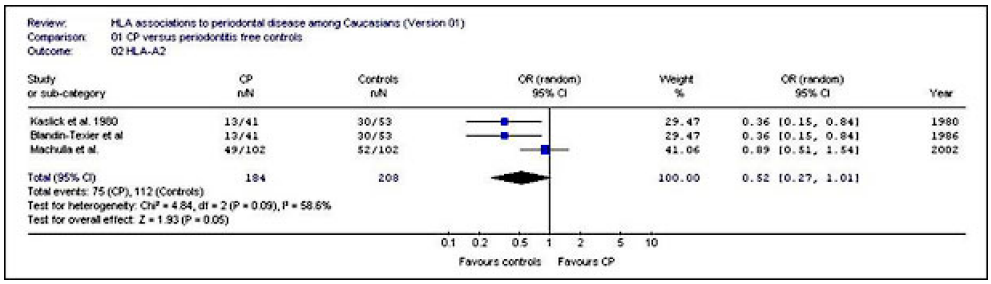

Fig 2: Combined analysis of HLA-A2 in patients with chronic periodontitis. CP = chronic periodontitis; OR = odds ratio

HLA-	Studies	Patients (Pf)	Controls (Pf)	Statistical Method	OR	P	95% CI
A1	2	31,10	29,45	Fixed Effects Model	1.09	0.74	0.67, 1.17
A2	3	40,76	53,85	Random Effects Model	0.52	0.05	0.27, 1.01
A3	2	21,95	30,14	Fixed Effects Model	0.65	0.10	0.39, 1.09
A9	3	27,32	22,61	Random Effects Model	1.36	0.54	0.51, 3.60
A10	2	9,15	8,22	Fixed Effects Model	1.14	0.74	0.52, 2.52
A11	2	12,20	8,22	Random Effects Model	1.30	0.33	0.27, 6.24
A29 (A19)	2	8,54	3,42	Fixed Effects Model	2.40	0.10	0.85, 6.83
A28	4	8,18	9,35	Fixed Effects Model	0.92	0.80	0.48, 1.77
>B15	3	15,12	11,06	Fixed Effects Model	1.37	0.30	0.76, 2.48
B18	3	9,38	9,63	Fixed Effects Model	1.00	1.00	0.50, 2.00
B5	4	7,25	14,85	Random Effects Model	0.42	0.21	0.11, 1.61
DR2	3	32,94	31,82	Fixed Effects Model	1.09	0.73	0.68, 1.74
DR3	3	21,18	20,13	Fixed Effects Model	1.08	0.79	0.63, 1.85
DR4	3	25,88	21,43	Random Effects Model	1.79	0.42	0.43, 7.42
DR5	3	21,18	21,43	Fixed Effects Model	0.99	0.96	0.57, 1.69
DR6	3	23,53	22,73	Fixed Effects Model	1.11	0.68	0.66, 1.88
DR7	3	20,00	20,78	Random Effects Model	1.02	0.98	0.31, 3.31
DR8	3	4,12	7,79	Fixed Effects Model	0.57	0.22	0.23, 1.40
DR9	3	1,76	2,60	Fixed Effects Model	0.66	0.55	0.17, 2.60
DR10	3	1,18	1,95	Fixed Effects Model	0.64	0.58	0.13, 3.22
DQ1	2	67,52	70,94	Fixed Effects Model	0.85	0.57	0.49, 1.49
DQ6 (DQ1)	2	45,30	41,88	Fixed Effects Model	1.16	0.58	0.68, 1.99
DQ2	2	32,48	35,04	Fixed Effects Model	0.89	0.68	0.52, 1.53
DQ3	2	52,99	49,57	Random Effects Model	1.63	0.48	0.42, 6.30

Tab 2: Combined analysis of HLA-antigen frequencies in patients with chronic periodontitis. Pf = phenotype frequency; OR = odds ratio; CI = confidence interval

HLA-	Studies	Patients (Pf)	Controls (Pf)	Statistical Method	OR	P	95% CI
A1	5	27,21	31,88	Fixed Effects Model	0.91	0.67	0.58, 1.41
A2	7	39,25	52,54	Fixed Effects Model	0.69	0.01	0.51, 0.93
A3	4	23,47	23,18	Fixed Effects Model	0.83	0.49	0.49, 1.41
A9	8	31,18	17,77	Random Effects Model	2.39	0.02	1.16, 4.92
A23 (A9)	4	6,15	3,28	Random Effects Model	1.54	0.50	0.44, 5.43
A24 (A9)	5	27,37	17,01	Random Effects Model	2.01	0.12	0.83, 4.88
A10	4	7,44	11,93	Random Effects Model	0.56	0.57	0.08, 4.10
A11	4	10,20	13,16	Fixed Effects Model	1.00	1.00	0.48, 2.09
A29 (A19)	3	6,98	4,82	Random Effects Model	2.51	0.35	0.36, 17.50
A30 (A19)				Random Effects			

	4	6,12	15,72	Model	0.93	0.94	0.14, 6.28
A31 (A19)	3	0,00	4,48	Fixed Effects Model	0.29	0.14	0.06, 1.49
A28	4	11,54	7,49	Fixed Effects Model	1.26	0.47	0.68, 2.34
B5	5	11,11	18,55	Fixed Effects Model	0.50	0.03	0.26, 0.95
B51 (B5)	3	9,30	12,24	Fixed Effects Model	0.70	0.38	0.31, 1.57
B52 (B5)	3	1,16	9,85	Fixed Effects Model	0.23	0.09	0.04, 1.23
B12	4	24,49	27,11	Random Effects Model	0.83	0.77	0.24, 2.87
B44 (B12)	3	25,58	20,60	Random Effects Model	1.29	0.61	0.50, 3.34
B45 (B12)	3	1,16	2,69	Fixed Effects Model	0.70	0.67	0.14, 3.50
B13	4	9,18	6,68	Fixed Effects Model	1.16	0.70	0.54, 2.51
B14	4	4,08	9,43	Fixed Effects Model	0.87	0.79	0.32, 2.35
B15	7	18,69	14,55	Random Effects Model	2.03	0.02	1.11, 3.72
B18	6	9,64	7,12	Fixed Effects Model	1.56	0.16	0.84, 2.89
B27	3	8,14	6,27	Fixed Effects Model	0.95	0.11	0.40, 2.29
B35	4	16,33	19,06	Fixed Effects Model	0.93	0.80	0.51, 1.69
B40	3	13,89	8,59	Fixed Effects Model	1.46	0.35	0.66, 3.25
DR1	3	10,47	16,42	Fixed Effects Model	0.49	0.07	0.22, 1.05
DR2	3	23,26	21,79	Fixed Effects Model	0.81	0.49	0.45, 1.46
DR3	3	15,12	9,25	Fixed Effects Model	1.29	0.49	0.62, 2.65
DR4	3	27,91	28,66	Random Effects Model	1.60	0.47	0.45, 5.69
DR5	4	28,46	16,75	Fixed Effects Model	1.27	0.28	0.83, 1.96
DR6	3	33,72	24,18	Fixed Effects Model	1.36	0.25	0.80, 2.32
DR7	3	31,40	31,64	Random Effects Model	0.90	0.83	0.35, 2.35
DR8	2	3,33	5,41	Fixed Effects Model	0.49	0.32	0.12, 1.98
DR9	2	3,95	1,40	Fixed Effects Model	2.64	0.22	0.56, 12.38
DR10	3	2,33	5,37	Fixed Effects Model	0.62	0.46	0.18, 2.18

Tab 3: Combined analysis of HLA-antigen frequencies in patients with aggressive periodontitis. Pf = phenotype frequency; OR = odds ratio; CI = confidence interval

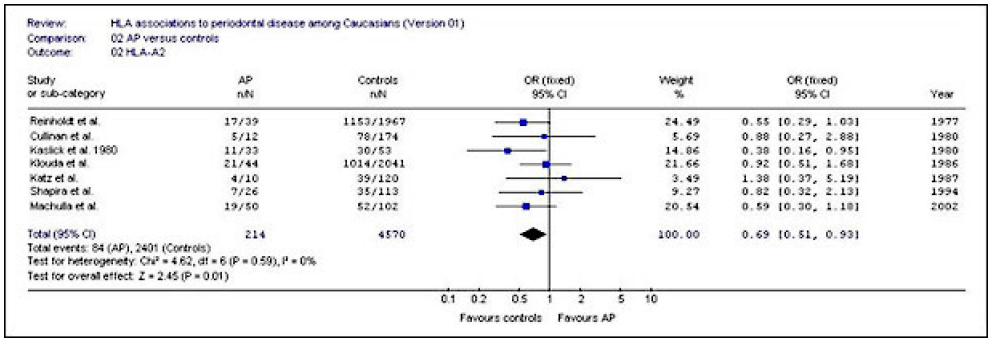

Fig 3: Combined analysis of HLA-A2 in patients with aggressive periodontitis. AP = aggressive periodontitis. OR = odds ratio

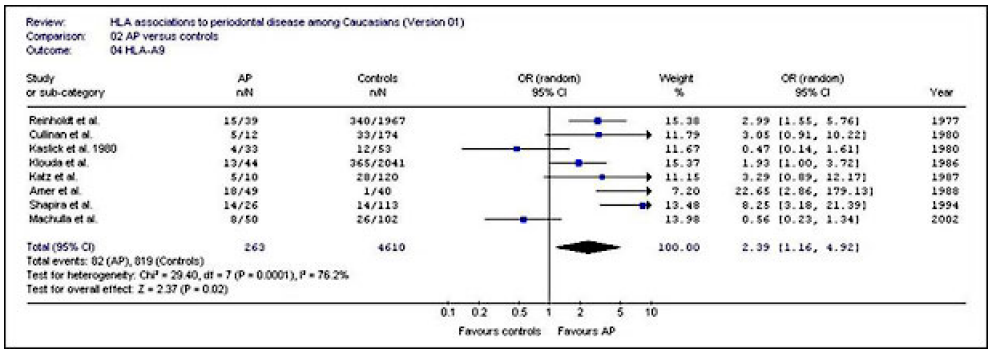

Fig 4: Combined analysis of HLA-A9 in patients with aggressive periodontitis. AP = aggressive periodontitis. OR = odds ratio

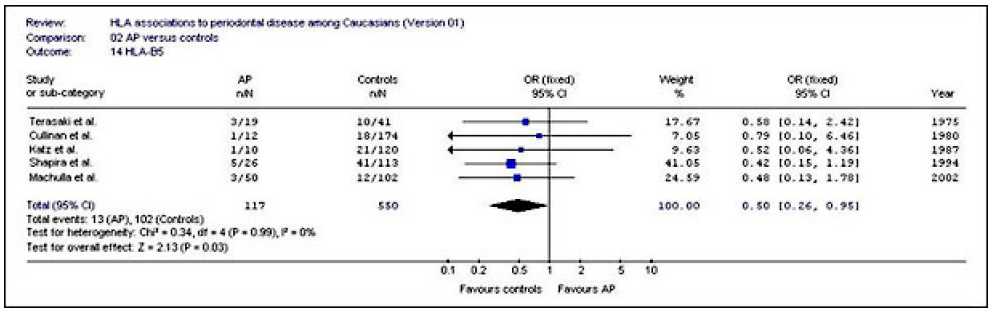

Fig 5: Combined analysis of HLA-B5 in patients with aggressive periodontitis. AP = aggressive periodontitis. OR = odds ratio

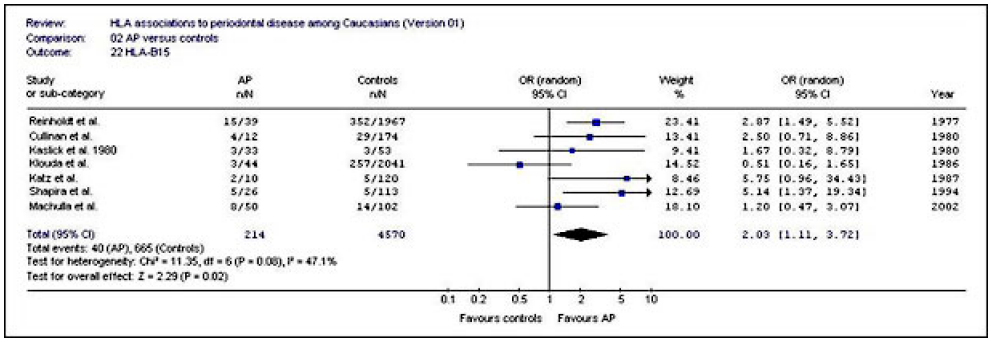

Fig 6: Combined analysis of HLA-B15 in patients with aggressive periodontitis. AP = aggressive periodontitis. OR = odds ratio

There is not enough data to demonstrate whether the associations of HLA-A9 and -B5 in aggressive periodon-titis were caused by association of only one or both of their split antigens (HLA-A23, -A24 and HLA-B51, -B52). It was not possible to evaluate deviations of HLA antigen frequencies between generalized and localized forms of aggressive periodontitis as only one study suitable for meta-analysis clearly defined criteria for localized aggres-sive periodontitis. The majority of included studies used a mixed patient group with both localized and generalized aggressive periodontitis.

Conclusions

This meta-analysis shows evidence that aggressive periodontitis among Caucasians is associated with HLA-A9 and -B15. These results are in accordance with previously published studies. In contrast, the negative association of HLA-B5 in aggressive periodontitis has not been noted before and might present a resistance factor for aggressive periodontitis. Moreover, our results confirm the formerly published negative association of HLA-A2 both in aggressive and chronic periodontitis suggesting a protective role for HLA-A2 towards periodontitis. HLA dependent T-cell restriction in recognition of antigen peptids and linkage disequilibrium between HLA genes and unknown suceptibility/resistance genes might explain the nature of these associations. Further studies should focus on subgroup and combination analyses of the associated HLA antigens as well as their associatons to peptides of periodontopathic bacteria in order to elucidate how these markers confer susceptibility or resistance to chronic and aggressive periodontitis.

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Abbreviations

MHC: major histocompatibility complex
HLA: human leukocyte antigens
PD: periodontal disease
CP: chronic periodontitis
AP: aggressive periodontitis
pf: phenotype frequency
OR: Odds Ratio

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