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Fcγ receptor polymorphisms and their association with periodontal disease: a meta-analysis

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Abstract

Aim: A systematic review and a meta-analysis were conducted in order to investigate the potential association of Fcγ receptor (FcγR) polymorphisms with susceptibility to aggressive and chronic periodontal disease.

Materials and Methods: A database search yielded a total of 17 studies involving 1685 cases and 1570 controls. Three polymorphisms were included in the meta-analysis: FcγRIIA H131R (rs1801274), FcγRIIIA F158V (rs396991) and FcγRIIIB NA1/NA2. Random-effect models were used in the analysis. Odds ratios (ORs) along with their 95% confidence intervals (CIs) were computed to compare the distribution of alleles and genotypes between cases and controls.

Results and Conclusions: The FcγRIIIB NA1/NA2 polymorphism was associated with both aggressive (per-allele OR 2.005, 95% CI: 1.044, 3.851) and chronic periodontitis (recessive contrast NA2NA2 *versus* NA1NA1+NA1NA2 OR 1.397, 95% CI: 1.039, 1.878). The analysis showed weak evidence for association between the FcγRIIA H131R polymorphism and aggressive periodontitis in Asians (R *versus* H allele OR 1.579, 95% CI: 1.025, 2.432). On the contrary, no relationship was identified between FcγRIIIA F158V and periodontal disease. Accumulating evidence from basic research makes the suggested association between FcγRIIIB NA1/NA2 polymorphism and periodontitis biologically plausible. Further research, however, is needed in order to assess possible gene–gene or gene–environment interactions (i.e. with smoking).

Keywords: Fcγ receptor; meta-analysis; periodontitis; polymorphism

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Periodontitis is an infectious disease of the supporting tissues of the teeth. The accumulation of bacteria in the gingival crevice might trigger an inflammatory process, which, if left untreated, destroys the periodontium and, eventually, results in tooth loss (Heitz-Mayfield 2005). The periodontal disease emerges either with the chronic or the aggressive form (Armitage 1999), and affects a significant portion of the population (Albandar et al. 1999, 2002, Bourgeois et al. 2007, Brothwell & Ghiabi 2009, Holtfreter et al. 2009). Although pathogenic microbes play an important role in the aetiology of periodontitis, the onset and progression of the disease is due to a combination of environmental and host-derived factors (Borrell & Papapanou 2005, Heitz-Mayfield 2005, Lang et al. 2009, Schatzle et al. 2009). Moreover, a considerable amount of evidence also supports the involvement of genetic factors in the pathogenesis of periodontal disease (Michalowicz et al. 2000, Kinane & Hart 2003, Nikolopoulos et al. 2008, de Carvalho et al. 2009, Gurkan et al. 2009, Raunio et al. 2009, Xie et al. 2009).

Fcγ receptors (FcγRs), which are membrane glycoproteins expressed on a wide variety of immune response cells, interact with the Fc (fragment, crystallizable) moiety of immunoglobulin G (IgG) molecules (Binstadt et al. 2003, Nimmerjahn & Ravetch 2006). FcγRs set thresholds for B cell activation, regulate the maturation of dendritic cells and they are involved in effector pathways such as the phagocytosis of opsonized microbes, the antibody-dependent

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cellular cytotoxicity and the release of inflammatory mediators (Nimmerjahn & Ravetch 2006). Currently, four classes of FcγRs [FcγRI (CD64), FcγRII (CD32) A/B/C, FcγRIII (CD16) A/B and FcγRIV] have been described with different affinities and isotype binding patterns (Binstadt et al. 2003, Nimmerjahn & Ravetch 2006).

Polymorphisms in genes encoding the FcγRs may result in variations in immune response and, thereby, might confer risk to many diseases (Kyogoku et al. 2002) including periodontitis (Sugita et al. 1999, Loos et al. 2003, Nares 2003). Three principal polymorphisms for the low-affinity receptors FcγRIIA, FcγRIIIA and FcγRIIIB have garnered particular attention: (i) A G to A (rs1801274) single nucleotide polymorphism (SNP) of the FCGR2A gene (location: 1q23) leads to the substitution of arginine (R) for histidine (H) at an amino acid position (denoted in literature as 131) in the extracellular domain of the FcγRIIA receptor (van der Pol & van de Winkel 1998, Binstadt et al. 2003). The H131 allotypic form interacts effectively with the complexed human IgG2, while the R131 protein binds poorly with this antibody subclass (Warmerdam et al. 1991); (ii) Subject of intense research is also the G/T SNP (rs396991) at position 559 (Ravetch & Perussia 1989) of the FCGR3A gene (location: 1q23) that causes the replacement of valine (V) with phenylalanine (F) at position 158 of the membrane-proximal Ig-like loop of FcγRIIIA (van der Pol & van de Winkel 1998, Binstadt et al. 2003). Other researchers have adopted a different nomenclature assigning position number 1 to the first amino acid of the precursor instead of the mature protein, that is, counting also the amino acids of the signal sequence. In this case, the nucleotide 559 is part of the codon for amino acid 176 of the precursor protein (Wu et al. 1997). The G/T polymorphism leads to changed affinities with the V158 allotype exhibiting significantly better binding capacity with IgG1/IgG3/IgG4 than does FcγRIIIA F158 (Koene et al. 1997, Wu et al. 1997); (iii) The glycosylphosphatidylinositol-linked FcγRIIIB exists in two isoforms, the neutrophil antigen 1 (NA1) and the neutrophil antigen 2 (NA2), as a consequence of many nucleotide substitutions resulting in alterations in four amino acids, which, in turn, produce different glycosylation patterns (Ory et al. 1989, van der Pol & van de Winkel 1998, Binstadt et al. 2003). The FcγRIIIB NA1 isotype displays a more efficient interaction with IgG1- and IgG3-opsonized bacteria and better phagocytic activity (Bredius et al. 1994, van der Pol & van de Winkel 1998).

Several research groups tried to gain further insight into the relevance of FcγR polymorphisms in the aetiology of periodontal disease, however, with conflicting results. Moreover, many individual studies had inadequate power to reveal mild gene effects because of their small sample sizes. Therefore, the current meta-analysis aimed to increase power by systematically combining the findings of previous research on the association between FcγR gene polymorphisms and susceptibility to periodontitis, and to explore the potential impact of between-study heterogeneity on the summary estimates.

Materials and Methods

Retrieval of published studies

Published studies that examined the association of the FcγR polymorphisms with periodontitis were considered. Electronic bio-medical databases such as Pubmed, Scopus and Google Scholar were searched using a combination of the terms ''periodontitis'', ''periodontal disease'', ''Fcgamma receptor'' and ''FcgammaR'' (last update search on October 2008). Full text publications and their reference lists were carefully screened to decide whether information on the topic of interest was included. The search was expanded by reviewing special meeting issues of journals in order to retrieve abstracts not included in computer indices.

Inclusion and exclusion criteria

Population-based case–control studies were eligible if they determined the distribution of genotypes for FcγR gene polymorphisms in periodontitis cases and in unrelated controls. Language or quality restrictions were avoided (Stroup et al. 2000, Pan et al. 2005). Furthermore, to eliminate the ''grey literature''-related bias (Conn et al. 2003), studies published in conference proceedings or as short abstracts were also considered.

Data extraction

The required information was extracted independently by two investigators (ND, PB) who discussed disagreements and reached consensus on all issues. The following data were sought from each report: (i) first author's name, journal, year of publication, ethnicity of participants and geographical setting; (ii) numbers of eligible genotyped cases and controls; (iii) the polymorphism under investigation and the disease form [aggressive (AP) or chronic periodontitis (CP)]; (iv) the distribution of genotypes and alleles in cases and controls; (v) average characteristics of the participants (age, sex, severity of the disease, smoking status, matching details, presence of a systemic disease or a medical condition) that could be used as covariates in a meta-regression model.

Statistical analysis

The odds ratio (OR) was the metric of choice. We examined the contrast of the mutant allele against the wild type and the contrasts of each group of homozygotes with the remaining subjects. In secondary analyses, we computed specific ORs for the Caucasian and Asian populations. Separate estimates according to the Hardy–Weinberg equilibrium (HWE) status of the control population were also calculated. The chi-squared method was applied to assess whether genotype frequencies in control groups were in HWE. For each genetic contrast, the between-study heterogeneity was evaluated using the Cochran's Q statistic (Petiti 1994) and the inconsistency index I^2 (Higgins et al. 2003).

Summary ORs along with their 95% confidence intervals (CIs) were estimated fitting conventional random-effects methods (DerSimonian & Laird 1986). Two recently proposed methodologies for the meta-analysis of gene–disease association studies were also applied: The multivariate random-effects method (Bagos 2008) and the random-effects logistic regression-based meta-analysis (Bagos & Nikolopoulos 2007). Both methods avoid multiple comparisons and test directly the genetic model of inheritance.

Publication bias was evaluated using the rank correlation method of Begg (Begg & Mazumdar 1994), the Egger's regression method (Egger et al. 1997) and its random-effects analogue (Thompson & Sharp 1999). Influential studies

were determined by checking the effect of removing an individual study each time on the overall significance of the estimate or on the heterogeneity statistic. Cumulative meta-analysis (Lau et al. 1992, Lau et al. 1995) was performed to assess whether the combined effect estimates changed as more evidence was accumulated (Ioannidis & Trikalinos 2005). A newly proposed regression-based method (Bagos & Nikolopoulos 2009) was used to detect a potential time trend in the summary estimates since the standard cumulative meta-analytic approach is based only on the rather subjective visual inspection of a graphical plot.

Analyses were conducted in the statistical package Stata 10 (Stata Corporation, College Station, TX, USA). Exempt for heterogeneity statistics (significance was declared if p-value <0.10), results were considered significant if the corresponding p-value was <0.05. All p-values were two tailed.

Results

The search of electronic databases yielded a total of 40 citations, the full text of which was examined in more detail (Fig. 1). Of these, 23 articles were excluded as shown in Table 1. Totally, 17 studies involving 1685 cases and 1570 controls were considered eligible (Table 2). Among them, 13 studies addressed more than one polymorphism. One publication (Komatsu et al. 2008) lacked the necessary data to assess the HWE and compute ORs in all contrasts. The control groups of three studies (Chung et al. 2003, Tang et al. 2004, Nibali et al. 2006) were not in HWE for the studied loci. One article (Tang et al. 2004) written in Chinese was retrieved and translated. Data on smoking habits were rather limited inhibiting the use of an established risk factor for periodontal disease, such as smoking, in a meta-regression model. Only one study reported data, on smoking stratified by genotype and disease status, that allow the evaluation of potential gene–environment interaction (Yamamoto et al. 2004). Only two studies reported data stratified by the severity of periodontal disease (Kobayashi et al. 2001a, Tang et al. 2004). Cumulative meta-analysis did not reveal any evidence for a trend in the effect estimates over time in any of the contrasts examined (data not shown).

FcγRIIA H131R (rs1801274)

Six studies evaluated the potential impact of the FcγRIIA H131R polymorphism on AP (Table 3). Among them, one study (Loos et al. 2003) enrolled Caucasians and two studies were conducted in an Asian population (Kobayashi et al. 2000a, Chung et al. 2003). The traditional summary-based methods produced insignificant ORs in most occasions except for the allele's comparison in the Asian subgroup (R *versus* H allele OR 1.579, 95% CI: 1.025, 2.432). The multivariate analysis yielded also non-significant estimates. Heterogeneity was moderate in the comparison of alleles ($I^2 = 61.6\%$). Formal statistical tests argued in favour of the absence of publication bias in all contrasts assessed.

A total of 11 studies, three in Caucasian populations (Loos et al. 2003, Yamamoto et al. 2004, Wolf et al. 2006) and eight that recruited subjects of Asian origin (Kobayashi et al. 1997, 2001a, 2003, Chung et al. 2003, Tang et al. 2004, Kobayashi et al. 2007a, 2007b, Komatsu et al. 2008) probed the association of FcγRIIA H131R polymorphism with CP (Table 3, Fig. 2). As was the case with AP, both the summary methods and the multivariate model yielded similar and insignificant results. Moderate between-study heterogeneity was observed only in the RR+HR *versus* HH contrast ($I^2 = 50.00\%$). Evidence for asymmetry in the funnel plot was detected only in the contrast of RR *versus* HH+HR genotypes by the three methods used (p-values <0.05). However, this is of no concern since the particular polymorphism was not found to confer a significant risk for CP.

FcγRIIIA F158V (rs396991)

The meta-analysis encompassed four studies that explored the association between the FcγRIIIA F158V polymorphism and AP (Table 4). The combined OR for the V allele *versus* the F allele was 1.026 (95% CI: 0.724, 1.456). In all analyses, including the multivari-

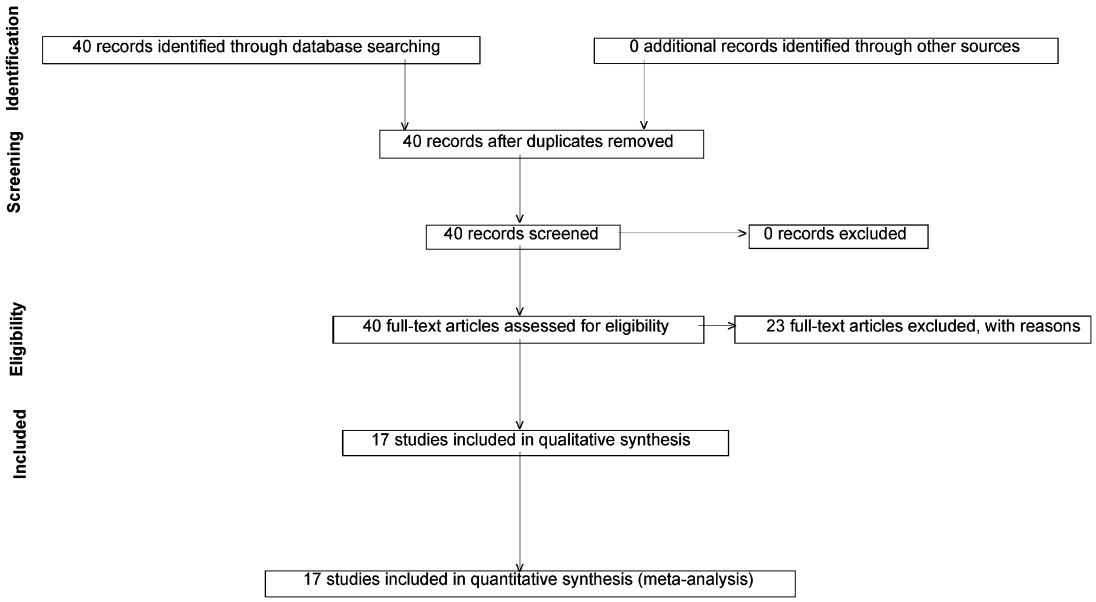

Fig. 1. Flow of information through the different phases of the meta-analysis.

Table 1. Studies excluded from the present meta-analysis along with the reason for exclusion

Study (reference)	Reasons for exclusion
1. Loos et al. (2008)	A review of genetics in periodontal disease
2. Yamamoto et al. (2007)	Evaluation of the intracellular expressions of IL-1β in CD14 positive cells upon stimulation with human IgG2 by flow cytometry
3. Johnstone et al. (2007)	This study does not examine the distribution of genotypes
4. Matthews et al. (2007b)	This study aims to determine whether neutrophil hyper-responsiveness was constitutive or reactive, and to discover the effect of non-surgical therapy
5. Matthews et al. (2007a)	This study investigates whether peripheral neutrophils from patients with chronic periodontitis generate higher levels of reactive oxygen species after Fcγ receptor stimulation than those from healthy controls
6. Naito et al. (2006)	It is not a case–control study
7. Loos et al. (2005)	A review of candidate genetic risk factors for periodontitis and possible mechanisms of action
8. Nagasawa et al. (2004)	This study does not examine the distribution of genotypes
9. Fredriksson et al. (2003)	Examination of the constitutionally hyper-reactive neutrophils in periodontitis
10. Meisel et al. (2001)	There are no controls
11. Kobayashi et al. (2001b)	It is not a case-control study
12. Kobayashi et al. (2000b)	This study examines the relevance of IgG receptor IIIb (CD16) polymorphism to handling of *Porphyromonas gingivalis*
13. Yuan et al. (1999b)	Determination of the levels of soluble Fcγ receptor III in gingival fluid from periodontal lesions
14. Fredriksson et al. (1999)	This study does not examine the distribution of genotypes
15. Yuan et al. (1999a)	It is not a case-control study
16. Yuan et al. (1998)	Determination of soluble Fcγ receptors in periodontal lesions
17. Colombo et al. (1998)	This study does not examine the distribution of genotypes
18. Fredriksson et al. (1998)	This study investigates the generation of chemiluminescence and intracellular hydrogen peroxide after in vitro priming and FcγR stimulation
19. Asman et al. (1997)	This study examines the expression of membrane molecules in periodontitis and gingivitis
20. Miyazaki et al. (1997)	This study examines the correlation between Fcγ RII and Fcγ RIII expressions and the phagocytic capacity of GCF-PMNs (gingival crevicular fluid)
21. Gustafsson & Asman (1996)	This study investigates the release of free oxygen radicals from peripheral neutrophils in adult periodontitis after Fcδ receptor stimulation
22. Wilson et al. (1995)	This study determines the IgG2 antibodies' capability of supporting phagocytosis and killing of *Actinobacillus actinomycetemcomitans* by human neutrophils
23. Okada et al. (1983)	This study is involved in the identification and distribution of immunocompetent cells in inflamed gingiva of humans with chronic periodontitis

Table 2. Characteristics of studies included in the present meta-analysis

Author	Year	Country	Cases	Controls	Form of Disease	Gene, Polymorphism
Kobayashi (Kobayashi et al. 1997)	1997	Japan	100	105	Chronic	Fcγ RIIIB NA1/NA2, Fcγ RIIA H131R
Sugita (Sugita et al. 1999)	1999	Japan	100	104	Chronic	Fcγ RIIIA F158V
Kobayashi (Kobayashi et al. 2000a)	2000	Japan	38	104	Aggressive	Fcγ RIIIB NA1/NA2, Fcγ RIIA H131R, Fcγ RIIIA F158V
Kobayashi (Kobayashi et al. 2001a)	2001	Japan	89	64	Chronic	Fcγ RIIIB NA1/NA2, Fcγ RIIA H131R, Fcγ RIIIA F158V
Yoshihara (Yoshihara et al. 2001)	2001	Japan	88	55	Aggressive, chronic	Fcγ RIIIB NA1/NA2
Fu (Fu et al. 2002)	2002	New Jersey	48	67	Aggressive	Fcγ RIIIB NA1/NA2, Fcγ RIIA H131R, Fcγ RIIIA F158V
Kobayashi (Kobayashi et al. 2003)	2003	Japan	42	42	Chronic	Fcγ RIIIB NA1/NA2, Fcγ RIIA H131R, Fcγ RIIIA F158V
Loos (Loos et al. 2003)	2003	Netherlands	68	61	Aggressive, chronic	Fcgamma RIIIB NA1/NA2, Fcγ RIIA H131R, Fcγ RIIIA F158V
Chung (Chung et al. 2003)	2003	Taiwan	78	74	Aggressive, chronic	Fcγ RIIIB NA1/NA2, Fcγ RIIA H131R
Yamamoto (Yamamoto et al. 2004)	2004	New York	213	209	Chronic	Fcγ RIIA H131R
Tang (Tang et al. 2004)	2004	China	166	80	Chronic	Fcγ RIIA H131R
de Souza (de Souza & Colombo 2006)	2006	Brazil	31	49	Aggressive	Fcγ RIIIB NA1/NA2, Fcγ RIIA H131R
Wolf (Wolf et al. 2006)	2006	Sweden	132	73	Chronic	Fcγ RIIIB NA1/NA2, Fcγ RIIA H131R
Nibali (Nibali et al. 2006)	2006	UK	221	231	Aggressive	Fcγ RIIIB NA1/NA2, Fcγ RIIA H131R, Fcγ RIIIA F158V
Kobayashi (Kobayashi et al. 2007b)	2007	Japan	58	44	Chronic	Fcγ RIIIB NA1/NA2, Fcγ RIIA H131R, Fcγ RIIIA F158V
Kobayashi (Kobayashi et al. 2007a)	2007	Japan	100	100	Chronic	Fcγ RIIIB NA1/NA2, Fcγ RIIA H131R, Fcγ RIIIA F158V
Komatsu (Komatsu et al. 2008)	2008	Japan	113	108	Chronic	Fcγ RIIIB NA1/NA2, Fcγ RIIA H131R

Table 3. Results of the meta-analysis of studies that evaluated the association between Fcγ RIIA H131R polymorphism and either aggressive or chronic periodontal disease

Contrast	Race	Number of studies	Number of cases/controls	Random effects odds ratio (*p*-value)	95% Confidence interval	Begg/Egger/random effects regression (*p*-values)	I^2 (*p*-value)
Fcγ RIIA H131R and aggressive periodontitis							
R allele *versus* H allele	All	6	374/586	1.002 (0.992)	0.695, 1.444	0.707/0.592/0.167	61.60% (0.023)
	Caucasian	1	12/61	0.272 (0.015)	0.095, 0.775	–	–
	Asian	2	65/178	1.579 (0.038)	1.025, 2.432	–	0.00% (0.747)
	Other	3	297/347	0.974 (0.865)	0.718, 1.320	–	30.60% (0.237)
RR genotype *versus* other (HH+HR) genotypes	All	6	374/586	1.067 (0.753)	0.711, 1.602	0.707/0.780/0.722	13.80% (0.326)
	Caucasian	1	12/61	0.131 (0.168)	0.007, 2.351	–	–
	Asian	2	65/178	2.143 (0.073)	0.931, 4.930	–	0.00% (1.000)
	Other	3	297/347	0.952 (0.791)	0.659, 1.375	–	0.00% (0.700)
Other (RR+HR) genotypes *versus* HH genotype	All	6	374/586	1.000 (0.999)	0.610, 1.639	0.260/0.512/0.223	54.80% (0.050)
	Caucasian	1	12/61	0.233 (0.027)	0.064, 0.844	–	–
	Asian	2	65/178	1.608 (0.117)	0.887, 2.914	–	0.00% (0.844)
	Other	3	297/347	0.991 (0.976)	0.559, 1.757	–	47.20% (0.150)
Fcγ RIIA H131R and chronic periodontitis							
R allele *versus* H allele	All	11	1117/960	1.073 (0.430)	0.900, 1.279	0.640/0.170/0.220	35.80% (0.113)
	Caucasian	3	401/343	0.872 (0.202)	0.706, 1.076	–	2.80% (0.357)
	Asian	8	716/617	1.189 (0.084)	0.977, 1.447	–	15.90% (0.305)
RR genotype *versus* other (HH+HR) genotypes	All	10	1004/852	1.245 (0.208)	0.885, 1.752	0.049/0.031/0.031	11.30% (0.339)
	Caucasian	3	401/343	1.056 (0.753)	0.751, 1.487	–	0.00% (0.559)
	Asian	7	603/509	1.810 (0.082)	0.927, 3.536	–	16.60% (0.303)
Other (RR+HR) genotypes *versus* HH genotype	All	10	1004/852	1.045 (0.770)	0.779, 1.400	0.371/0.097/0.097	50.00% (0.035)
	Caucasian	3	401/343	0.679 (0.019)	0.492, 0.938	–	0.00% (0.533)
	Asian	7	603/509	1.252 (0.155)	0.919, 1.705	–	29.60% (0.202)

We list the results obtained with the random effects method (OR and 95% CI), the *p*-values from the three tests of publication bias (Begg's, Egger's and random effects regression) as well as the I^2 and *p*-value for heterogeneity.

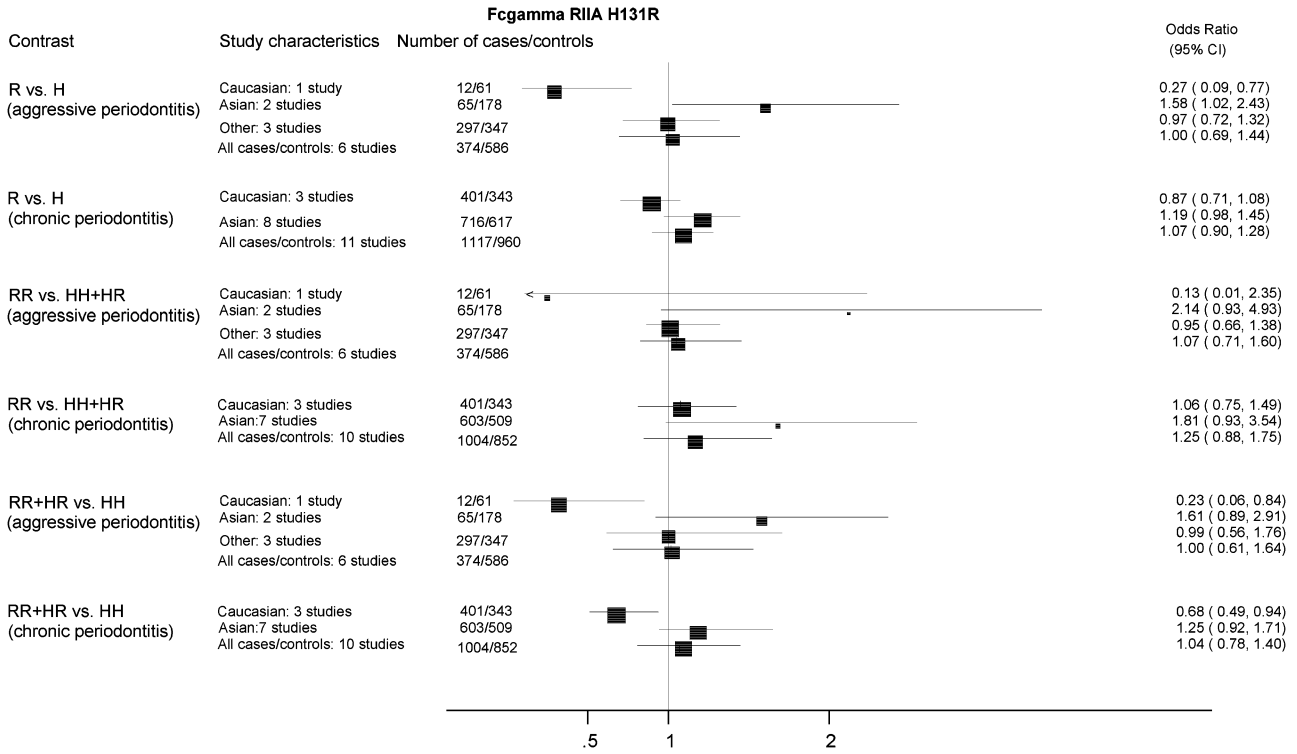

Fig. 2. Graphical representation for the results of the meta-analysis concerning the association of Fcγ RIIA H131R polymorphism with chronic and aggressive periodontitis.

Table 4. Results of the meta-analysis of studies that evaluated the association between the Fcγ RIIIA F158V polymorphism and either aggressive or chronic periodontal disease

Contrast	Race	Number of studies	Number of cases/controls	Random effects odds ratio (p-value)	95% Confidence interval	Begg/Egger/random effects regression (p-values)	I^2 (p-value)
Fcγ RIIIA F158V and aggressive periodontitis							
V allele *versus* F allele	All	4	316/461	1.026 (0.884)	0.724, 1.456	0.734/0.597/0.281	43.30% (0.152)
	Caucasian	1	12/61	2.569 (0.040)	1.042, 6.337	–	–
	Asian	1	38/104	0.924 (0.793)	0.510, 1.672	–	–
	Other	2	266/296	0.942 (0.638)	0.736, 1.207	–	0.00% (0.369)
VV genotype *versus* other (FF+FV) genotypes	All	4	316/461	1.072 (0.735)	0.716, 1.606	0.734/0.481/0.549	0.00% (0.722)
	Caucasian	1	12/61	2.042 (0.302)	0.526, 7.924	–	–
	Asian	1	38/104	1.106 (0.872)	0.325, 3.761	–	–
	Other	2	266/296	0.994 (0.981)	0.634, 1.561	–	0.00% (0.552)
Other (VV+FV) genotypes *versus* FF genotype	All	4	316/461	0.926 (0.814)	0.490, 1.752	1.000/0.832/0.684	49.20% (0.116)
	Caucasian	1	12/61	7.639 (0.059)	0.926, 62.992	–	–
	Asian	1	38/104	0.848 (0.668)	0.401, 1.797	–	–
	Other	2	266/296	0.708 (0.468)	0.278, 1.802	–	49.20% (0.161)
Fcγ RIIIA F158V and chronic periodontitis							
V allele *versus* F allele	All	6	445/415	1.062 (0.629)	0.833, 1.353	0.707/0.592/0.618	21.50% (0.272)
	Caucasian	1	56/61	1.598 (0.077)	0.951, 2.684	–	–
	Asian	5	389/354	0.970 (0.799)	0.768, 1.225	–	0.00% (0.491)
VV genotype *versus* other (FF+FV) genotypes	All	6	445/415	0.941 (0.796)	0.594, 1.492	0.707/0.627/0.642	0.00% (0.508)
	Caucasian	1	56/61	1.633 (0.262)	0.693, 3.849	–	–
	Asian	5	389/354	0.752 (0.307)	0.436, 1.299	–	0.00% (0.726)
Other (VV+FV) genotypes *versus* FF genotype	All	6	445/415	1.119 (0.421)	0.851, 1.470	0.452/0.376/0.335	0.00% (0.456)
	Caucasian	1	56/61	1.898 (0.108)	0.869, 4.145	–	–
	Asian	5	389/354	1.039 (0.795)	0.777, 1.391	–	0.00% (0.613)

We list the results obtained with the random effects method (OR and 95% CI), the p-values from the three tests of publication bias (Begg's, Egger's and random effects regression) as well as the I^2 and p-value for heterogeneity.

ate model (OR for FV *versus* FF contrast: 0.909, 95% CI: 0.649, 1.275; OR for VV *versus* FF contrast: 0.988, 95% CI: 0.626, 1.561), insignificant estimates were derived. Between-study heterogeneity was not evident in most comparisons. All relative statistical tests showed no evidence for publication bias.

Regarding the role of FcγRIIIA F158V polymorphism in CP, a total of six studies were included (Table 4, Fig. 3). One research group studied individuals of Caucasian descent (Loos et al. 2003), while the remaining five studies concentrated on Asian populations (Sugita et al. 1999, Kobayashi et al. 2001a, 2003, 2007a, 2007b). The summary OR corresponding to the comparison of alleles (V *versus* F) was 1.062 (95% CI: 0.833, 1.353). Similar insignificant results without considerable heterogeneity or publication bias were observed in the other analyses. Furthermore, the application of the multivariate method yielded ORs of 1.171 (95% CI: 0.857, 1.599) and 0.995 (95% CI: 0.569, 1.738) for the FV *versus* FF and VV *versus* FF contrasts, respectively.

FcγRIIIB NA1/NA2 polymorphism

Totally, seven studies examined the association between the FcγRIIIB NA1/NA2 polymorphism and AP (Table 5). Among them, three studies focused on Asian populations (Kobayashi et al. 2000a, Yoshihara et al. 2001, Chung et al. 2003) and one study included subjects of Caucasian origin (Loos et al. 2003). The per-allele OR was 2.005 with a 95% CI: 1.044, 3.851. The estimate was slightly larger (OR 2.118, 95% CI: 1.029, 4.361) in the comparison of NA2 homozygotes (NA2NA2 carriers) with subjects carrying other genotypes (NA1NA1+NA1NA2). The application of the multivariate meta-analytic approach yielded insignificant estimates. However, the ratio of the natural logarithms of these ORs (denoted by λ) was 0.521, implying a co-dominant model of inheritance, a result compatible with the significant estimate derived from the alleles contrast. Publication bias was absent in most analyses, while, on the other hand, there was considerable evidence for heterogeneity.

Overall, 10 studies investigated the effect of FcγRIIIB NA1/NA2 polymorphism on CP (Table 5, Fig. 4). Only two research teams (Loos et al. 2003, Wolf et al. 2006) recruited Caucasians. A significant estimate was observed (OR 1.397, 95% CI: 1.039, 1.878) in the NA2NA2 *versus* NA1NA1+NA1NA2 contrast. Under the multivariate framework, the OR obtained from the NA2NA2 *versus* NA1NA1 contrast was also significant (1.442, 95% CI: 1.025, 2.029) and λ was close to zero (0.137) with a standard error of 0.329. Therefore, both the summary-based method and the multivariate technique suggested a recessive model of inheritance. Heterogeneity was not detected in all comparisons and no substantial evidence of publication or other small study-related bias was found in the analyses.

Discussion

Human FcγRs create an important link between humoral and cellular defence mechanisms. One or more FcγR-mediated functions of immune cells may become less efficient or, on the contrary, overefficient because of polymorphisms in genes encoding FcγRs. Three subclasses of human IgG receptors have been shown to be functionally polymorphic. Therefore, many research groups explored the potential effect of FcγR polymorphisms on the occurrence of various inflammatory and infectious diseases including periodontitis, which is determined by the host immune response

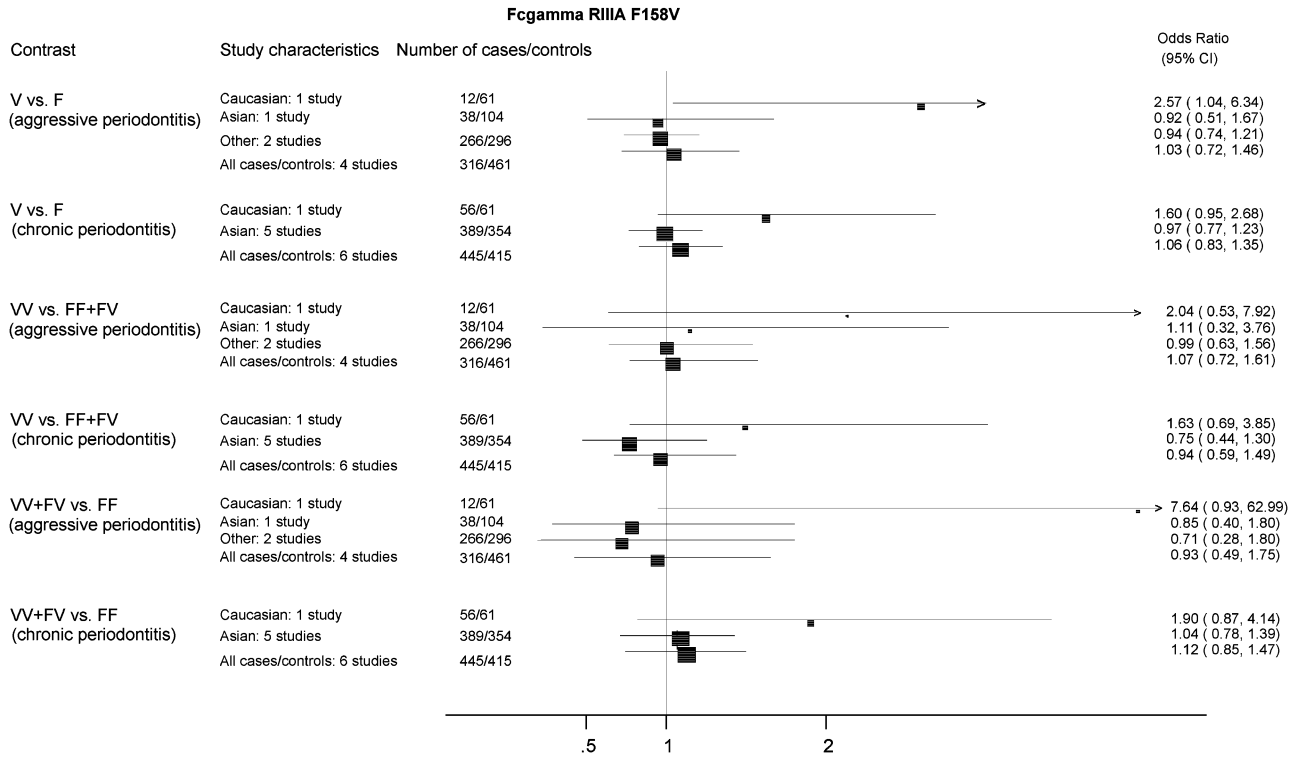

Fig. 3. Graphical representation for the results of the meta-analysis concerning the association of Fcγ RIIIA F158V polymorphism with chronic and aggressive periodontitis.

Table 5. Results of the meta-analysis of studies that evaluated the association between the Fcγ RIIIB NA1/NA2 polymorphism and either aggressive or chronic periodontal disease

Contrast	Race	Number of studies	Number of cases/ controls	Random effects odds ratio (*p*-value)	95% Confidence interval	Begg/Egger/random effects regression (*p*-values)	I^2 (*p*-value)
Fcγ RIIIB NA1/NA2 and aggressive periodontitis							
NA2 allele *versus* NA1 allele	All	7	414/641	2.005 (0.037)	1.044, 3.851	0.368/0.081/0.057	89.10% (0.000)
	Caucasian	1	12/61	0.783 (0.598)	0.315, 1.945	–	–
	Asian	3	102/233	1.810 (0.019)	1.102, 2.970	–	50.20% (0.134)
	Other	3	300/347	3.425 (0.105)	0.772, 15.200	–	95.60% (0.000)
NA2NA2 genotype *versus* other (NA1NA1+NA1NA2) genotypes	All	7	414/641	2.118 (0.042)	1.029, 4.361	0.548/0.109/0.067	68.20% (0.004)
	Caucasian	1	12/61	0.630 (0.486)	0.171, 2.315	–	–
	Asian	3	102/233	3.284 (0.001)	1.635, 6.598	–	0.00% (0.975)
	Other	3	300/347	2.524 (0.158)	0.698, 9.128	–	82.00% (0.004)
Other (NA2NA2+NA1NA2) genotypes *versus* NA1NA1 genotype	All	7	414/641	2.344 (0.083)	0.893, 6.149	0.133/0.094/0.480	86.40% (0.000)
	Caucasian	1	12/61	0.982 (0.987)	0.104, 9.246	–	–
	Asian	3	102/233	2.093 (0.049)	1.003, 4.370	–	46.00% (0.157)
	Other	3	300/347	3.360 (0.258)	0.412, 27.409	–	94.70% (0.000)
Fcγ RIIIB NA1/NA2 and chronic periodontitis							
NA2 allele *versus* NA1 allele	All	10	792/726	1.132 (0.103)	0.975, 1.313	0.152/0.160/0.252	0.00% (0.771)
	Caucasian	2	188/134	0.914 (0.595)	0.658, 1.271	–	0.00% (0.722)
	Asian	8	604/592	1.195 (0.036)	1.012, 1.411	–	0.00% (0.830)
NA2NA2 genotype *versus* other (NA1NA1+NA1NA2) genotypes	All	9	679/618	1.397 (0.027)	1.039, 1.878	0.602/0.334/0.500	0.00% (0.906)
	Caucasian	2	188/134	1.023 (0.922)	0.644, 1.627	–	0.00% (0.597)
	Asian	7	491/484	1.730 (0.005)	1.177, 2.542	–	0.00% (1.000)
Other (NA2NA2+NA1NA2) genotypes *versus* NA1NA1 genotype	All	9	679/618	1.135 (0.311)	0.888, 1.450	0.754/0.978/0.978	0.00% (0.622)
	Caucasian	2	188/134	0.642 (0.218)	0.317, 1.300	–	0.00% (0.958)
	Asian	7	491/484	1.227 (0.124)	0.945, 1.594	–	0.00% (0.760)

We list the results obtained with the random effects method (OR and 95% CI), the *p*-values from the three tests of publication bias (Begg's, Egger's and random effects regression) as well as the I^2 and *p*-value for heterogeneity.

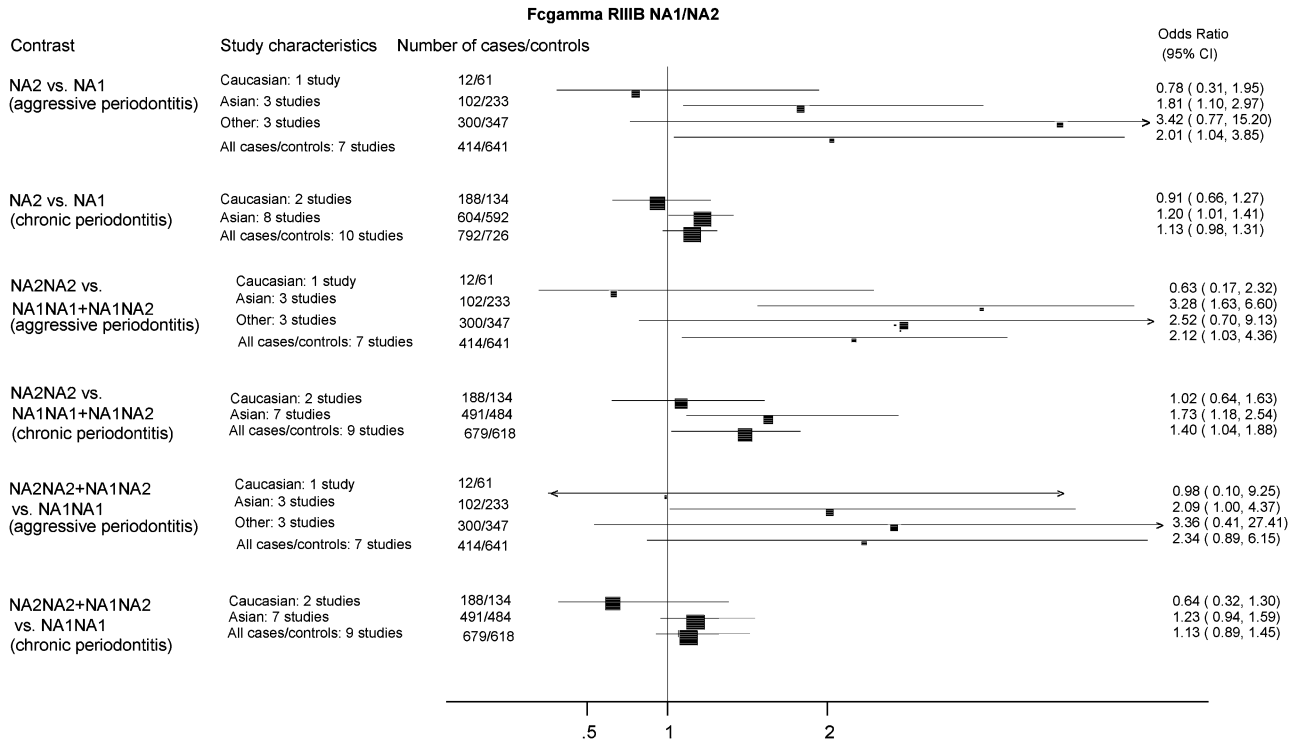

Fig. 4. Graphical representation for the results of the meta-analysis concerning the association of Fcγ RIIIB NA1/NA2 polymorphism with chronic and aggressive periodontitis.

against periodopathic microbes. The current meta-analysis summarizing the results of 17 previous studies in the field shows an association between the FcγRIIIB NA1/NA2 gene polymorphism and periodontal disease. More specifically, the NA2 allele seems to double the risk for AP, a finding that is more prominent for NA2 homozygotes. Moreover, the present report also documents an elevated risk for CP of NA2 homozygotes. On the other hand, the remaining FcγR polymorphisms, apart from the weak association between the FcγRIIA H131R polymorphism and aggressive periodontal disease in Asian populations, were not found to affect significantly the susceptibility to either CP or AP.

Accumulating evidence from basic research makes the association between the FcγRIIIB NA1/NA2 gene polymorphism and periodontal disease biologically plausible. The most abundantly found phagocyte, the polymorphonuclear leucocyte (PMN), expresses the polymorphic FcγRIIA and FcγRIIIB receptors (Bredius et al. 1994). With respect to the FcγRIIIB polymorphism in neutrophils, studies in the early 1990s demonstrated its functional significance. More specifically, the PMNs of individuals carrying the NA2 allele have shown reduced phagocytic capacity for FcyRIII-dependent probes (IgG-sensitized erythrocytes and concanavalin A-treated erythrocytes) (Salmon et al. 1990). These different properties were extended to biologically relevant antibodies since the NA2NA2 PMNs exhibited lower IgG1-mediated phagocytosis of bacteria, and monoclonal IgG3 anti-D-mediated rosette formation and phagocytosis than PMNs homozygous for NA1 (Bredius et al. 1994). FcγRIII-bearing cells have been detected in inflamed gingival tissue of patients with periodontal disease (Yuan et al. 1999a). The uptake of IgG-opsonized bacteria through FcγRs on PMNs comprises a central defence mechanism in periodontium and various disorders of neutrophil function are associated with severe destruction of periodontal tissue (Kinane & Hart 2003). The concept of the involvement of the FcγRIIIB NA1/NA2 gene polymorphism in periodontal disease became more evident when IgG1- and IgG3-opsonized *Porphyromonas gingivalis*, a Gram-negative anaerobe implicated in periodontal disease, were found to be less effectively phagocytosed by NA2 PMNs (Kobayashi et al. 2000b). Moreover, the same research group showed that the induction of oxidative burst on interaction with IgG1- and IgG3-opsonized *P. gingivalis* was reduced in NA2-carrying PMNs (Kobayashi et al. 2000b).

Some shortcomings of the analysis should be discussed. Periodontitis is a complex disease, and modifying factors such as smoking might possibly have an effect on genetic associations with periodontitis phenotypes. However, we were not capable of conducting genotype-stratified analyses due to the lack of properly reported sufficient data from the primary studies. Second, the statistical synthesis of gene–disease association studies in the field of periodontology pertains to many biases because of the small number of subjects enrolled in individual studies, the heterogeneity in periodontitis definition, the performance of multiple tests and the inappropriate selection of controls (Borrell & Papapanou 2005). Nevertheless, we invested a great deal of efforts in limiting possible source of bias by avoiding any form of quality scoring (Greenland 1998), searching for reports not included in electronic databases (Conn et al. 2003), retrieving eligible non-English articles (Pan et al. 2005), assessing the effect of HWE violations

(Trikalinos et al. 2006), applying multivariate meta-analytic techniques (Bagos 2008, Bagos & Nikolopoulos 2007), performing statistical tests for detecting publication bias (Egger et al. 1997, Sterne et al. 2000) and evaluating the existence of a time trend in the summary estimates (Ioannidis et al. 2001).

Allowing for the limitations listed above, the meta-analysis suggests that the FcγRIIIB NA1/NA2 gene polymorphism is an important factor associated with susceptibility to periodontitis. However, unlike simple genetic traits, an individual genetic variant is not sufficient to cause a complex disease such as periodontitis. Combining a few disease-associated alleles, even with moderate effects, may lead to estimates of periodontitis risks with considerable clinical utility (Ioannidis et al. 2006). For instance, a previous study that focused on the genetic aetiology of AP found an increased effect of FcγRIIIB NA2 allele when it was combined with a specific variant in the vitamin D receptor gene (Yoshihara et al. 2001). Future research should emphasize on the potential interaction of the FcγRIIIB NA1/NA2 gene polymorphism with other genetic variations such as the interleukin-1A 889T and interleukin-1B 3953/4T polymorphisms (Nikolopoulos et al. 2008), and the TLR4 Asp299Gly and Thr399Ile polymorphisms (Ozturk & Vieira 2009), which are also implicated in the pathogenesis of periodontal disease.

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Clinical Relevance

Scientific rationale for the study: Conflicting results have been presented in the past concerning the role of a genetic component in the susceptibility to periodontitis and several SNPs of the FcγR genes have been implicated.

Principal findings: With this meta-analysis, we present for the first time evidence that the FcγRIIIB NA1/NA2 polymorphism is significantly associated with chronic as well as with aggressive periodontal disease, whereas the FcγRIIA H131R polymorphism slightly affects the occurrence of AP in Asian populations.

Practical implications: The results presented here may have implications in screening and prevention of periodontal disease.