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Identification of genetic risk factors for periodontitis and possible mechanisms of action

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Abstract

Aim: To review the literature for genetic risk factors associated with periodontitis.

Methods: Computerized search of the literature in English using key words: Periodontitis; Genes; Mutation; Polymorphism; Risk.

Results and Conclusions: Mutations in the cathepsin C gene (*CTSC*) have been identified as causal for the Papillon–Lefèvre syndrome (PLS), which includes prepubertal periodontitis (PP). Some *CTSC* mutations are causal for PP without PLS. No relationship has been demonstrated between *CTSC* mutations and other forms of periodontitis. Genetic polymorphisms in a candidate gene approach have been explored as risk factors for periodontitis. There is limited evidence that some polymorphisms in the genes encoding interleukins (IL)-1, Fcgamma receptors (FcγR), IL-10 and the vitamin D receptor, may be associated with periodontitis in certain ethnic groups. However relatively large variations in carriage rates of the *Rare* (*R*)-alleles among studies on any polymorphism were observed. The available studies appear under-powered and do not adequately take into account other pertinent risk factors for periodontitis. Future studies should include larger cohorts, should clearly define phenotypes and should adequately control for other risk factors. In addition to the candidate gene approach, alternative strategies need to be considered to elucidate the gene variations, which confer risk for periodontitis.

Key words: FcγR; genetics; IL-1; IL-10; periodontitis; risk factors; VDR

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Periodontitis is a chronic infectious disease of the supporting tissues of the teeth. Due to the bacterial infection, the periodontal tissues become inflamed and are slowly destroyed by the action of the inflammatory process. If left untreated, the teeth lose their ligamentous support to the alveolar bone, become mobile and are eventually lost.

Periodontitis is considered to be a complex disease. Common features of complex human diseases (e.g. Alzheimer's disease, Crohn's disease and cardiovascular diseases) are that these conditions present mostly with a relatively mild phenotype and are slowly progressive and chronic in nature (Tabor et al. 2002). Furthermore, these types of diseases are of relatively late onset (i.e. adolescent or adult onset) and relatively common. The pathophysiology of complex diseases is characterized by various biological pathways, leading to similar clinical phenomena. Importantly, complex diseases are associated with variations in multiple genes, each having a small overall contribution and relative risk for the disease process; complex diseases are typically polygenic (Tabor et al. 2002). The disease genes in complex diseases are therefore considered disease modifying genes (Hart et al. 2000b). Analogous to other complex diseases, we estimated that for periodontitis, at least 10 and as high as 20 modifying disease genes may be involved. However, it is important to realize that the number and type of modifying disease genes for the same condition may not be equal for different ethnic populations; they are also influenced by environmental factors (gene–environment interactions).

Disease modifying genes contrast to major disease genes. Aberrant allelic forms of major genes are responsible for disease expression according to Mendel's laws (Hart et al. 2000b). For example, the fatal inherited disease cystic fibrosis caused by a recessive mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (Brennan & Geddes 2002). This gene encodes for a protein that functions as a plasma membrane chloride channel in epithelial tissues, in particular in lung epithelium. If a person is homozygous for the *Rare* disease allele (*R*-allele), then he/she will develop cystic fibrosis. On the other hand, individuals will not

develop the disease if they are homozygous for the *normal* (*N*) allele (so called *wild type*) or when they are heterozygous, i.e. they have both the dominant *N*-allele and the recessive *R*-allele.

Genetic risk factors have been proposed to influence the natural history of periodontitis (Michalowicz et al. 1991, Hart 1994, Hart & Kornman 1997, Hart et al. 1997, Page 1999, Hart et al. 2000b, Page & Sturdivant 2002). The presence of a genetic risk factor directly increases the probability of periodontal disease developing, and, if absent, reduces this possibility. Genetic risk factors are part of the causal chain, or expose the host to the causal chain. Notably, it may be possible that an allele, which is originally defined as *R*-allele, is associated with absence of disease; in such cases, the genetic factor could be considered protective.

In this paper we explore current literature on putative genetic risk factors. From the late 1990s a substantial increase in papers on putative genetic risk factors for susceptibility to and severity of periodontitis has appeared in the periodontal literature. However, some investigators in the early 1990s (Michalowicz et al. 1991, Hart 1994) proposed genetic risk factors for periodontitis.

Evidence for the Role of Genetics in Periodontitis

Several papers have reviewed the strong suggestion that periodontitis has a genetic basis (Hart & Kornman 1997, Hart et al. 1997, Michalowicz et al. 2000, Hart et al. 2000b, Loos & Van der Velden 2003). Briefly, for early-onset periodontitis (EOP) it was recognized from family studies several years ago that siblings of patients with juvenile periodontitis (JP) frequently also suffered from periodontitis. It was suggested by some authors that the most likely mode of inheritance was autosomal dominant in both African-American and Caucasian kindred, with 70% penetrance in African-Americans and 73% in Caucasians (Marazita et al. 1994).

Very few investigations have utilized family studies of probands with chronic (adult) periodontitis or younger subjects with mild/incipient periodontitis. One study investigated the effect of sibling relationship on the periodontal condition in a group of young Indonesians deprived of regular dental care (Van der Velden et al. 1993). The results suggested that there may also be a genetic basis for the less severe forms of periodontitis. In epidemiological studies in the Dutch population it has been suggested that chronic (adult) periodontitis aggregates in families (Van der Velden et al. 1989, Petit et al. 1994).

The twin model is probably the most powerful method to study genetic aspects of periodontal diseases. Michalowicz and co-workers evaluated the periodontal condition (attachment loss, pocket depth, gingival index and plaque index) of 110 adult twin pairs with a mean age of 40 years, ranging from 16 to 70 years (Michalowicz et al. 1991). The results indicated that between 38% and 82% of the population variance for these measures may be attributed to genetic factors. In a study on 117 adult twin pairs the analysis included the evaluation of environmental factors like smoking and utilization of dental services (Michalowicz et al. 2000). From the results the authors estimated that chronic (adult) periodontitis had approximately 50% heritability, which was unaltered following adjustments for behavioural variables including smoking. In contrast, while monozygotic twins were also more similar than dizygotic twins for gingivitis scores, there was no evidence of heritability for gingivitis after behavioural covariates such as utilization of dental care and smoking were incorporated in the analysis.

From both the twin studies and familial studies it can be concluded that the basis for familial aggregation of periodontitis appears to be genetic rather than bacterial, environmental, or behavioural in nature.

Definitions and Strategy

Variant forms (polymorphisms) of a gene that can occupy a specific chromosal site (*locus*) are called *alleles*. Two or more alleles for a given locus may exist in nature throughout evolution, but may develop at any time. A *polymorphic* locus is one whose alleles are such that the most common, *normal* variant (*N*-allele) among them occurs with $<99\%$ frequency in the population. Thus, if a locus is for example *bi-allelic*, the rarer allele (designated *R*-allele) must occur with a frequency $>1\%$ in the population. In this way, when different alleles of a given gene co-exist in the human population, we speak about *genetic polymorphisms*.

Polymorphisms arise as a result of gene mutations. All organisms undergo spontaneous mutations as a result of normal cellular function or random interactions with the environment. An alteration that changes only a single base pair is called a point mutation. Not all point mutations are repaired and can therefore be transmitted by inheritance through generations. The most common class of point mutations is the *transition*, comprising the substitution of a G–C (guanine–cytosine) pair with an A–T (adenine–thymine) pair or vice versa. The variation at the site harboring such changes has recently been termed a ''single nucleotide polymorphism'' (SNP) (Schork et al. 2000).

The SNP may have no effects or may have some important biological effects. For example, if a transition has taken place within the coding region of a gene, it may result in an amino acid substitution and therefore an altered protein structure, which may then alter its function. Or, when such mutations have taken place in the promoter region of the gene, it may alter gene regulation, for example resulting in (completely) inhibited or reduced gene expression or, alternatively, result in over-expression of the gene, perhaps with biological consequences. SNPs occur more frequently than any other type of genetic polymorphism; the frequency of SNPs across the human genome is estimated at every 0.3–1 kilobases (kb) (Schork et al. 2000).

Other types of genetic polymorphisms result from *insertions* or *deletions* (Schork et al. 2000). The simple form of this polymorphism is where a single nucleotide pair may be deleted or may be inserted with the same potential effects as described above for the transition. The most common type of insertion/deletion polymorphism is the existence of variable numbers of repeated bases or nucleotide patterns in a genetic region. Repeated base patterns can consist of several hundreds of base pairs, known as ''variable number of tandem repeats'' (VNTRs or *mini-satellites*). Also common are *micro-satellites*, which consist of 2, 3 or 4 nucleotide repeats, on a variable number of occasions. Micro-satellites are also referred to as *simple tandem repeats* (STRs). Such repeats are considered highly polymorphic and often result in many alleles or gene variants due to the existence of many different repeat sizes within the population. The STRs may

occur every 3–10 kb genome wide (Schork et al. 2000).

Genetic polymorphisms are very useful in studies of population genetics. After genotyping individuals and assessing genotype frequencies among groups of interest, one can also calculate the frequency of the *N*-allele and the *R*-allele among the groups or populations under study. Frequencies of genotypes and alleles may differ between a diseased group and a healthy group. Subsequently, when a given allele is identified to be associated with disease, functional studies can be started to investigate the possible role of that gene in the aetiology and pathogenesis of the disease.

From the current review, it became clear that the number of studies and the sample sizes for a given putative genetic risk factor were too small to draw definitive conclusions on allele frequencies in Caucasian or Japanese or any other populations. Therefore in this review we have limited ourselves to presenting in the tables the frequency of the carriage rate of the *R*-allele (frequency of *N/R* and *R/R* genotypes) among cases and controls. From this tabulation, it can be seen that at this point there is relatively large variation among the various studies for the *R*-allele carriage rate, even if the study populations are of the same ethnic background. Future meta-analyses, when larger studies are available, can be performed to determine allele frequencies in the various global populations. This approach will ultimately enable us to determine to what extent a population is at risk for that disease and to what extent population based screening is useful.

In the preparation of this review, we encountered various nomenclatures for the diagnosis of cases and controls, and, during the years, the nomenclature for the diagnosis of the various forms of periodontitis has changed. In this paper, we have used the diagnosis of periodontitis from the original manuscripts as much as possible.

This review focuses mainly on putative genetic risk factors that have been identified by the candidate gene approach, i.e. investigators have plausible arguments of a conceptual, biological and epidemiological nature to investigate the association of the selected genetic polymorphism(s) with periodontitis. Nevertheless, by linkage analysis in specific families with several generations available and having among them one or more proband(s) with a strong disease phenotype, new disease genes may still be identified. Before the candidate genes and their respective genetic polymorphisms are explored in their association with periodontitis, we first discuss the discovery of a major disease gene associated with pre-pubertal periodontitis and the Papillon–Lefèvre syndrome (PLS).

A Gene Mutation of Major Effect on Human Disease and its Association with Periodontitis

Periodontitis is observed as a component of many single gene syndromes (Kinane & Hart 2003). Many of these disorders are characterized either by immune or structural deficiencies; of these syndromic disorders, the PLS is relatively unique, in that periodontitis forms a significant component of the disease and indeed, is one of two defining clinical features.

The gene mutated in PLS was mapped to a specific band on the long arm of chromosome 11 (Fischer et al. 1997, Laass et al. 1997, Hart et al. 1998). Subsequently, this location was refined and a candidate gene within this region was identified that encoded for the lysosomal protease cathepsin C: the *CTSC* gene (Toomes et al. 1999). They elucidated its genomic organization, demonstrated mutations in the *CTSC* gene in eight families and showed that these mutations result in an almost complete loss of function of the enzyme. This was immediately confirmed (Hart et al. 1999) and Hart and co-workers demonstrated similar mutations in further families. To date more than 40 mutations have been reported in the *CTSC* gene (Selvaraju et al. 2003, de Haar et al. 2004, Noack et al. 2004). Furthermore, interesting data from analyses in a single family with four different *CTSC* mutations were reported (Hewitt et al. 2004) and the investigators proposed that minimal cathepsin C activity ($\sim$ 13%) was necessary to prevent the clinical features of PLS.

CTSC mutations have also been identified in families with pre-pubertal periodontitis suggesting that this condition is allelic to PLS (Hart et al. 2000a). However, these mutations are not different to those observed in classical PLS and, notably, all cases of pre-pubertal periodontitis do not have mutations in *CTSC*. This suggests that pre-pubertal periodontitis is a genetically heterogeneous condition with some cases representing a variant of PLS (Hewitt et al. 2004). There has also been speculation that polymorphic functional variants of *CTSC* may be involved in the more common type of non-familial aggressive periodontitis. However, given that carriers of a mutant copy of the gene are phenotypically unaffected and that very little cathepsin C activity appears to be necessary in order to preventing the disease, this seems an unlikely hypothesis. Indeed, evidence against this hypothesis was provided (Hewitt et al. 2004); it was shown that there was no difference in cathepsin C activity between 30 cases of aggressive periodontitis and controls.

Modifying Disease Genes in Relation to Periodontitis

Periodontitis develops in a limited subset of humans. About 10–15% of the population will develop severe forms of destructive periodontal disease. The disease is importantly influenced by the microorganisms in the subgingival biofilm, by acquired systemic diseases that reduce or hamper an ''optimal'' host response, and by environmental factors. Specific bacteria in the microbial biofilm and smoking are accepted as true rather than putative risk factors. On top of the above risk factors are modifying disease genes, which contribute to susceptibility and severity of periodontitis. For these disease modifying genes, Mendelian principles do not apply (Hart 1996, Hart et al. 2000b) because both heterozygous as well as homozygous subjects for a given disease modifying gene may not necessarily develop the disease; other genetic risk factors (gene–gene interactions) and/or environmental risk factors (gene–environmental interactions) also need to be present simultaneously (definition of complex disease).

Currently, very little is known about which genes may be involved in periodontitis as disease modifying genes. Table 1 summarizes the candidate gene polymorphisms investigated in relation to periodontitis. It is clear from this summary that, as the immune system plays a crucial role in the pathogenesis of periodontitis, researchers have concentrated on the identification of genetic polymorphisms in several aspects of host immunity.

Below we discuss the epidemiological findings in various studies of candidate genes as risk factors. We have

Table 1. Summary of candidate genes, and the corresponding encoded proteins, for which gene polymorphisms have been investigated as putative risk factors for periodontitis

Gene	Coded protein
ACE	Angiotensin-converting enzyme
CARD15 (*NOD2*)	Caspase recruitment domain-15 (NOD2)
CCR5	Chemokine receptor-5
CD14	CD-14
ER2	Estrogen receptor-2
ET1	Endothelin-1
FBR	Fibrinogen
FcγRIIa	Fc γ receptor IIa
FcγRIIb	Fc γ receptor IIb
FcγRIIIa	Fc γ receptor IIIa
FcγRIIIb	Fc γ receptor IIIb
FPR1	*N*-formylpeptide receptor-1
IFNGR1	Interferon γ receptor-1
IL1A	Interleukin-1α
IL1B	Interleukin-1β
IL1RN	Interleukin-1 receptor antagonist
IL2	Interleukin-2
IL4	Interleukin-4
IL6	Interleukin-6
IL10	Interleukin-10
LTA	Lymphotoxin-α
MMP1	Matrix metalloproteinase-1
MMP3	Matrix metalloproteinase-3
MMP9	Matrix metalloproteinase-9
MPO	Myeloperoxidase
NAT2	N-acetyltransferase-2
PAI1	Plasminogen-activator-inhibitor-1
RAGE	Receptor for advanced glycation end products
TGFB	Transforming growth factor-β
TIMP2	Tissue inhibitor of matrix metalloproteinase
TLR2	Toll-like receptor-2
TLR4	Toll-like receptor-4
TNFA	Tumor necrosis factor-α
TNFR2	Tumor necrosis factor receptor-2
VDR	Vitamin D receptor

grouped some candidate genes together and mention possible mechanisms of action, i.e. which arguments have been used and which hypotheses have been proposed to study the various modifying genes in relation to periodontitis.

IL-1 and TNF-α gene polymorphisms

There are several arguments used to justify why the genes encoding for interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) appear to be good candidates for genetic studies of periodontitis (Cox & Duff 1996, Kornman et al. 1997, Verweij 1999, Craandijk et al. 2002):

(1) There is evidence to suggest that *IL1* and *TNFA* play important roles in the pathogenesis of periodontitis. IL-1α, IL-1β and TNF-α are potent immunologic mediators with proinflammatory properties (Graves & Cochran 2003). Moreover, IL-1 and TNF-α have the capacity to stimulate bone resorption and they can regulate fibroblast cell proliferation of both gingival and periodontal ligament origin (Taubman & Kawai 2001, Graves & Cochran 2003). IL-1 and TNF-α levels are increased in the gingival crevicular fluid of periodontitis subjects and these cytokines are found in higher levels in inflamed periodontal tissues compared to healthy tissues (Stashenko et al. 1991, Ishihara et al. 1997).

(2) Various studies have suggested that polymorphisms in the genes of the *IL1* cluster and in the *TNFA* gene could predispose subjects to elevated IL-1 [decreased IL-1 receptor antagonist (RA)] and TNF-α protein levels (Pociot et al. 1992, Danis et al. 1995, Andus et al. 1997, Wilson et al. 1997, Higuchi et al. 1998, Santtila et al. 1998, Tountas et al. 1999, Dominici et al. 2002, El-Omar et al. 2003). The majority of these cited studies suggest that the *R*-allele of a given polymorphism in the promoter region results in an upregulation of protein production. These studies have often been performed with isolated cells of healthy individuals or with cultured cell-lines or cell constructs (transfected cells).

(3) Inherent (most likely genetically determined) inter-individual differences have also been observed for IL-1 and TNF-α production by peripheral blood mononuclear cells or oral leukocytes, isolated from individuals with and without periodontitis. It is conceivable that these differences in IL-1 and TNF-α production and secretion play a role as risk factors. For example, periodontitis patients carrying the *R*-allele of *IL1B* +3953 were shown to have increased production of IL-1β by activated peripheral blood neutrophilic polymorphonuclear leukocytes (neutrophils/PMNs), although this increase failed to reach statistical significance (Gore et al. 1998). Gingival crevicular fluid (GCF) levels of IL-1β and TNF-α, and gingival tissue levels of IL-1α, IL-1β and TNF-α were determined in non-smoking adult patients (>35 years) with periodontitis and related to their *IL1* genotype (Engebretson et al. 1999). GCF samples were collected at baseline and 3 weeks following conservative treatment and analysed by ELISA for IL-1β and TNF-α. An interproximal gingival biopsy was collected at baseline and follow-up and also analysed for IL-1α, IL-1β and TNF-α by ELISA. Prior to treatment, in shallow sites (<4 mm), IL-1β in GCF was 2.5 times higher for those patients carrying simultaneously an *R*-allele at *IL1A* −889 and at *IL1B* +3954 (*IL1* composite genotype *ad modum* Kornman et al. (1997), see below for further details) than in those not having the *IL1* composite genotype; in these sites after treatment, IL-1β in GCF was still 2.2 times higher for the *IL1* composite genotype patients. These differences were less apparent in deeper sites. Thus, following treatment, a reduction in IL-1β concentration in GCF was seen for those patients being *IL1* composite genotype negative, while this was not

seen for *IL1* composite genotype positive patients. These data suggest that patients carrying the *IL1* composite genotype may demonstrate phenotypic differences as indicated by elevated levels of IL-1β in GCF (Engebretson et al. 1999).

In 32 patients with periodontitis and 32 controls, levels of TNF-α production by oral PMNs were measured in relation to the *TNFA* -308 polymorphism (Galbraith et al. 1998). The periodontitis patients carrying the *R*-allele at position -308 of the *TNFA* gene, had higher TNF-α production by oral PMNs than the non-carriers; interestingly this was not found among the controls. However, it is important to consider that TNF production by oral PMNs is determined following priming of these cells with subgingival bacteria, before they were cultured (Galbraith et al. 1998).

In another study (Galbraith et al. 1999), the authors not only investigated the prevalence of the *IL1* composite genotype, but they also studied PMNs obtained through mouth rinses and obtained from peripheral blood for their capacity to produce IL-1β in relation to the underlying genotype. In this study, 20 patients (15 smokers) with advanced periodontitis and 20 gingivitis subjects (three smokers) participated. These investigators found the IL-1β production to be higher in the advanced periodontitis patients in comparison to gingivitis subjects, but no significant correlation was observed between genotype and cytokine production. Nevertheless, there was a trend towards increased IL-1β production by oral PMNs in patients carrying the *R*-allele of the *IL1* composite genotype in comparison to non-carriers patients (Galbraith et al. 1999). However, in these studies the effect of smoking and gender could play a role and additional studies are needed which take these aspects into consideration.

The concept that *IL1* composite genotype patients would have an intrinsically higher IL-1β production has also been challenged (Mark et al. 2000). In the latter study, peripheral blood monocytes were obtained from 10 adult periodontitis patients carrying the composite *IL1* genotype and 10 age-matched patients negative for the *IL1* composite genotype. Monocytes were cultured with a panel of bacterial stimuli. The results demonstrated that monocytes from *IL1* composite genotype positive and genotype negative patients showed no significant differences in IL-1β production in response to any stimulant tested. In addition, the periodontal pathogens *Porphyromonas gingivalis*, *Tannerella forsythensis* and *Prevotella intermedia* failed to stimulate higher IL-1β responses compared to health-associated species *Veilonella parvula* and *Streptococcus sanguis*. A marked inter-individual variation in production of IL-1β was seen, with high, low and intermediate responders present in both *IL1* composite genotype positive and composite genotype negative subjects (Mark et al. 2000).

Among 128 Japanese individuals, comprising 64 patients with severe adult periodontitis and 64 healthy subjects, the prevalences of SNPs in the *TNFA* gene promoter (at positions -1031, -863, -857, -308, -238) and in the *IL1B* gene (at positions -511, -31, $+3953$) were determined (Soga et al. 2003). In a small subgroup (15 healthy male subjects), production of TNF-α and IL-1β by *Escherichia coli* lipopolysaccharide (LPS)-stimulated peripheral blood monocytes was determined. No differences in IL-1β production between the carriers and non-carriers of the *R*-allele for the *IL1B* -511 were found (Soga et al. 2003). However, it is important to note that the host cell stimulatory properties of *E. coli*-LPS may differ from those of Gram-negative periodontal bacteria.

In summary, there are indications that the studied polymorphisms in the *IL1* and *TNFA* genes may be associated with altered levels of IL-1β and TNF-α; however, insufficient evidence currently exists to conclude that this is a key phenomenon occurring in the pathophysiology of periodontitis. Nevertheless, the concept is attractive and may explain some of the epidemiological findings of genetic polymorphisms associated with the susceptibility to and severity of periodontitis.

(4) Some *IL1* and *TNFA R*-alleles have been suggested as potential genetic markers for complex diseases. For example, *IL1* and *TNFA* gene polymorphisms have been associated with several inflammatory and infectious disease processes, including inflammatory bowel disease, Sjögren syndrome, rheumatoid arthritis, meningococcal disease, systemic lupus erythematosus and psoriasis (Perrier et al. 1998, Jouvenne et al. 1999, Buchs et al. 2001, Magnusson et al. 2001, Reich et al. 2002, Vatay et al. 2003, Balding et al. 2004, Muraki et al. 2004).

Epidemiological findings for gene polymorphisms in the IL1 gene cluster

The genes encoding for the proteins IL-1α, IL-1β and IL1-RA are located in close proximity in the *IL1* gene cluster on chromosome 2. Kornman et al. (1997) reported first on polymorphisms for the *IL1* genes in relation to periodontitis. This study reports on an *IL1* composite genotype (see below); however, no data are presented for the carriage rates of the individual *IL1 R*-alleles (*IL1A*, *IL1B*, *IL1RN*). To date, the following *IL1* genetic polymorphisms have been studied in relation to periodontitis: *IL1A* -889 (in linkage disequilibrium with $+4845$), *IL1B* -511 (in linkage disequilibrium with -31), *IL1B* $+3954$ (also mentioned in the literature as $+3953$) and *IL1RN* VNTR. Results for case–control studies in Caucasians and non-Caucasians are presented in Tables 2–6. The tables present the number of subjects included, their ethnic origin, the periodontal disease diagnosis and the prevalences of *R*-allele carriage rates for periodontitis patients and controls, as well as whether in the cited reference an association with periodontitis and/or the severity of periodontitis has been found.

From the tables it becomes clear that among the different studies with exclusively Caucasian subjects, considerable variation is seen for the carriage rates of the *IL1 R*-alleles. For example for the polymorphic *IL1A* -889 ($+4845$) (Table 2), the carriage rate for the *R*-allele varies from 34% to 64% for patients and 35–60% for controls. None of the studies involving Caucasians and non-Caucasians have found a significant association between periodontitis and/or disease severity and *IL1A* -889 ($+4845$) as single risk factor, except when combined with

Table 2. Carriage of the *Rare* (*R*)-allele at position *IL1A* −889 (+4845), mainly in case–control studies, and the association with periodontitis

Reference	Ethnicity of subjects	Patients			Controls		Associated with periodontitis	Associated with severity of periodontitis
		Diagnosis of cases	*n*	*R*-allele carriage (%)	*n*	*R*-allele carriage (%)		
Gore et al. (1998)	Caucasian	AP	32	43	32	38	–	–
Shirodaria et al. (2000)*	Mixed	CP	83	69	37	52	–	n.t.
Hodge et al. (2001)	Caucasian	G-EOP	56	34	56	35	–	n.t.
Laine et al. (2001)	Caucasian	AP	105	64	53	60	– (+†)	n.t.
Rogers et al. (2002)	Caucasian	CP	69	48	60	45	–	n.t.
Meisel et al. (2002a)	Caucasian	CP	154	56			n.t.	–
Gonzales et al. (2003)	Caucasian	AgP	28	46	33	40	–	n.t.
Sakellari et al. (2003)	Caucasian	CP	45	53	110	43	–	n.t.
D'Aiuto et al. (2004)‡	Mixed	CP	94	61			n.t.	– (+§)
Tai et al. (2002)	Japanese	G-EOP	47	21	97	19	–	n.t.
Quappe et al. (2004)	Chilian	AgP	36	44	75	40	–	n.t.
Anusaksathien et al. (2003)	Thai	Mixed status	123	15			–	n.t.
Li et al. (2004a)	Chinese	G-AgP	122	14	95	12	– (+¶)	n.t.

*Mixed population: 63% Caucasian; 22% Asian; 15% Afro-Caribbean.

†An association with periodontitis was found for combined genotype: carriage of *R*-allele for *IL1A* −889, IL-1B +3954 and *IL1* RN in a subgroup of patients being non-smokers, and at the same time culture negative for *P. gingivalis* and *A. actinomycetemcomitans.*

‡Mixed population: 65% Caucasian; 20% Asian; 15% African or Afro-Caribbean.

§Elevated levels of IL-6 in serum associated with *R*-allele.

¶*R*-allele associated with periodontitis in males.

AP, adult periodontitis; CP, chronic periodontitis, not further specified in the study; G- or L-EOP, generalized or localized early-onset periodontitis; GJP or LJP, generalized or localized juvenile periodontitis; (L)-AgP, (localized) aggressive periodontitis; n.t., not tested; −, association not found; +, association found.

Table 3. Carriage rate of the *Rare* (*R*)-allele at gene and position *IL1B* −511 (−31), mainly in case–control studies, and the association with periodontitis

Reference	Ethnicity of subjects	Patients			Controls		Associated with periodontitis	Associated with severity of periodontitis
		Diagnosis of cases	*n*	*R*-allele carriage (%)	*n*	*R*-allele carriage (%)		
Gore et al. (1998)	Caucasian	AP	32	59	32	59	–	–
D'Aiuto et al. (2004)*	Mixed	CP	94	63			n.t.	–
Tai et al. (2002)	Japanese	G-EOP	47	72	97	68	–	n.t.
Soga et al. (2003)	Japanese	Severe AP	64	67	64	78	–	n.t.
Li et al. (2004a)	Chinese	G-AgP	122	73	95	71	– (+†)	n.t.

Abbreviations and symbols as in Table 2.

*Mixed population: 65% Caucasian; 20% Asian; 15% African or Afro-Caribbean.

†*R*-allele associated with periodontitis when combined with smoking.

other factors such as other *IL1* polymorphisms, gender, microbiology and/or smoking status. The carriage rate of the *IL1A* −889 (+4845) *R*-allele in Chileans was comparable to that reported by other reports (Quappe et al. 2004), while the carriage rate among Japanese appears lower (Tai et al. 2002). The latter finding demonstrates an important issue, that is that carriage rate of genetic polymorphisms may vary among different ethnic populations. Therefore, possible positive associations between a genetic polymorphism and disease within one population may not necessarily be extrapolated to other populations.

Three studies have reported carriage rates for the *IL1B* −511 (−31) *R*-allele, and, to date, this genetic polymorphism has not been associated with periodontitis (Table 3). The carriage of the *R*-allele was higher among Japanese (67–78%) than among Caucasians (59%) (Gore et al. 1998, Tai et al. 2002, Soga et al. 2003).

The SNP *IL1B* +3954 (+3953) initially appeared promising as risk factor for periodontitis among Caucasians (Table 4). However there are conflicting results. Galbraith et al. (1999) found an association between the *R*-allele and periodontitis and Gore et al. (1998) observed an association with the severity of periodontal destruction. Quappe et al. (2004) reported that the *N*-allele might indeed be protective for periodontitis in Chileans. By contrast, Parkhill et al. (2000) observed among early-onset periodontitis (EOP) patients an over-representation of the *N*-allele, and they concluded that the *N*-allele, and in particular in smokers, is associated with periodontitis, rather than the *R*-allele. The latter observation was also shown in a family linkage analysis, which included both families of African-American and Caucasian heritage, therefore implying a role in the disease process for the *N*-allele (Diehl et al. 1999). Among Japanese subjects, the carriage rate of the *IL1B* +3954 (+3953) is importantly low (<10%), given this low carriage rate, and no association with periodontitis was found (Table 4). Clearly, large-scale studies in homogeneous populations are needed to

Table 4. Carriage rate of the *Rare* (*R*)-allele at gene and position *IL1B* +3954 (+3953), mainly in case–control studies and association with periodontitis

Reference	Ethnicity of subjects	Patients			Controls		Associated with periodontitis	Associated with severity of periodontitis
		Diagnosis of cases	*n*	*R*-allele carriage (%)	*n*	*R*-allele carriage (%)		
Gore et al. (1998)	Caucasian	AP	32	43	32	38	–	+
Galbraith et al. (1999)	Caucasian	AP	40	50	45	27	+	–
Hodge et al. (2001)	Caucasian	G-EOP	56	31	56	31	–	n.t.
Parkhill et al. (2000)	Caucasian	EOP	91	41	72	60	– (+*)	n.t.
Laine et al. (2001)	Caucasian	AP	105	49	53	45	– (+†)	n.t.
Meisel et al. (2002a)	Caucasian	CP	154	48			n.t.	–
Sakellari et al. (2003)	Caucasian	CP	45	49	110	50	–	n.t.
Rogers et al. (2002)	Caucasian	CP	69	35	60	40	–	n.t.
Gonzales et al. (2003)	Caucasian	AP	28	46	33	48	–	n.t.
D'Aiuto et al. (2004)§	Mixed	CP	94	32			n.t.	–
Tai et al. (2002)	Japanese	G-EOP	47	4	97	9	–	n.t.
Soga et al. (2003)	Japanese	Severe AP	64	6	64	10	–	n.t.
Anusaksathien et al. (2003)	Thai	Mixed status	123	2			–	n.t.
Quappe et al. (2004)	Chilian	AgP	36	31	75	16	–‡	n.t.
Li et al. (2004a)	Chinese	G-AgP	122	7	95	2	–	n.t.

Abbreviations and symbols as in Table 2.
*Association of *N*-allele with periodontitis and *R*-allele protective in smokers.
†An association with periodontitis was found for combined genotype: carriage of *R*-allele for *IL1A* −889, *IL1B* +3954 and *IL1* RN in a subgroup of patients being non-smokers and, at the same time, culture negative for *P. gingivalis* and *A. actinomycetemcomitans.*
‡Homozygosity for *N*-allele is protective for periodontitis.
§Mixed population: 65% Caucasian; 20% Asian; 15% African or Afro-Caribbean.

Table 5. Carriage rate of the *Rare* (*R*)-allele for gene *IL1RN* (VNTR), mainly in case–control studies and association with periodontitis

Reference	Ethnicity of subjects	Patients			Controls		Associated with periodontitis	Associated with severity of periodontitis
		Diagnosis of cases	*n*	*R*-allele carriage (%)	*n*	*R*-allele carriage (%)		
Parkhill et al. (2000)	Caucasian	EOP	70	31	72	49	– (+*)	n.t.
Laine et al. (2001)	Caucasian	AP	105	46	53	38	– (+†)	n.t.
Meisel et al. (2002a)	Caucasian	CP	154	36			n.t.	– (+‡)
Tai et al. (2002)	Japanese	G-EOP	47	26	97	8	+	n.t.
Li et al. (2004a)	Chinese	G-AgP	122	15	95	18	–	n.t.

Abbreviations and symbols as in Table 2.
**N*-allele combined with carriage of *N*-allele for *IL1B* +3954 was associated with EOP.
†An association with periodontitis was found for combined genotype: carriage of *R*-allele for *IL1A* −889, *IL1B* +3954 and *IL1RN* (VNTR) in a subgroup of patients being non-smokers and culture negative for *P. gingivalis* and *A. actinomycetemcomitans.*
‡Combination with *R*-allele *IL1A* −889 in smokers.

further investigate the potential of the *IL1* +3954 (+3953) genotypes as risk factors for periodontitis.

Few studies have investigated polymorphisms in the *IL1RN* gene, encoding the *IL-1RA* (Table 5) and, again, conflicting results are reported. In Caucasians the *R*-allele was not associated as a single risk factor with periodontitis, however in combination with other factors and *IL1* SNPs it was reported to have a possible relationship with periodontitis prevalence and severity (Laine et al. 2001, Meisel et al. 2002b). In Japanese, the *IL1RN R*-allele was significantly associated with periodontitis (Tai et al. 2002). In contrast, Parkhill et al. (2000) observed the *IL-1RN N*-allele in combination with the *IL1B* +3954 *N*-allele and smoking to be associated with EOP.

Kornman et al. (1997) reported that the combined presence of the *R*-allele of the *IL1A* gene at nucleotide position −889 and the *R*-allele of the *IL1B* gene at nucleotide position +3954 (+3953) was associated with severity of periodontitis in non-smoking Caucasian patients. This combined carriage rate of the *R*-alleles was designated the *IL1* composite genotype (Kornman et al. 1997). Since that time a considerable number of studies investigating the *IL1* composite genotype has been published in Caucasians and non-Caucasians (Table 6). An association between the *IL1* composite genotype and the severity of periodontal destruction has also been reported by 2 other cross-sectional studies (McDevitt et al. 2000, Papapanou et al. 2001). However, other studies have failed to corroborate that *IL1* composite genotype alone may behave as a risk factor for periodontitis severity (Gore et al. 1998, Ehmke et al. 1999, Cattabriga et al. 2001, Meisel et al. 2002b, 2003, 2004). In contrast to the results of Kornman et al. (1997), Meisel et al. (2002a, 2002b, 2003, 2004) observed the *IL1* composite genotype to be associated with periodontitis in smokers. These conflicting results cast doubt on the utility of the *IL1* composite genotype as a putative risk factor for severity of periodontitis in Caucasians.

Table 6. *IL1* composite genotype *ad modum* Kornman et al. (1997) (i.e. *Rare* (*R*)-allele at genes and positions *IL1A* −889 (+4845) and *IL1B* +3954 (+3953)), mainly in case–control studies, and association with periodontitis

Reference	Ethnicity of subjects	Patients			Controls		Associated with periodontitis	Associated with severity of periodontitis
		Diagnosis of cases	*n*	Genotype positive (%)	*n*	Genotype positive (%)		
Kornman et al. (1997)	Caucasian	AP	99*	36			n.t.	+
Gore et al. (1998)	Caucasian	AP	32	34	32	28	–	–
McGuire & Nunn (1999)†	Caucasian	CP	42	38			n.t.	+
Ehmke et al. (1999)	Caucasian	CP	33	48			n.t.	–
McDevitt et al. (2000)‡	Caucasian	CP	44	41	46	28	+	n.t.
McDevitt et al. (2000)‡	Caucasian	CP	90	34			n.t.	+
Hodge et al. (2001)	Caucasian	G-EOP	56	46	56	46	–	n.t.
Laine et al. (2001)	Caucasian	AP	105	46	53	42	–	n.t.
Papapanou et al. (2001)	Caucasian	EOP	132	45	73	45	–	+
Cattabriga et al. (2001)†	Caucasian	CP	60	38			n.t.	–
Thomson et al. (2001)	Caucasian	CP	61	28	800	33	–	n.t.
Cullinan et al. (2001)†	Caucasian	CP	295	39			– (+§)	n.t.
Meisel et al. (2002a)	Caucasian	CP	154	44			n.t.	– (+¶)
Sakellari et al. (2003)	Caucasian	CP	45	44	110	38	–	n.t.
Rogers et al. (2002)	Caucasian	EOP and AP	69	29	60	30	–	n.t.
Meisel et al. (2003)	Caucasian	CP	402	38	414	34	– (+¶)	n.t.
Gonzales et al. (2003)	Caucasian	AgP	28	36	33	33	–	n.t.
Meisel et al. (2004)	Caucasian	CP	1085	36	–	–	n.t.	– (+¶)
Armitage et al. (2000)	Chinese	CP	300	2			–	–
Walker et al. (2000)	African-American	LJP	37	8	104	14	–	n.t.
Anusaksathien et al. (2003)	Thai	Mixed status	123	2			–	n.t.
Gonzales et al. (2003)	Hispanic	AP	16	25	14	21	–	n.t.
Quappe et al. (2004)	Chilian	AgP	36	25	75	12	–	n.t.

Abbreviations and symbols as in Table 2.

*Only non-smokers were included.

†Longitudinal.

‡Eighty-two per cent of study population is of Caucasian heritage; results found after multiple logistic regression analysis correcting for smoking status and age.

§In subjects >50 years and non-smokers.

¶In smokers.

After the initial encouraging results of Kornman et al. (1997), mainly case–control studies have investigated the *IL1* composite genotype as a putative risk factor for periodontitis and mostly in Caucasian populations (Table 6). One study observed an association between the *IL1* composite genotype and periodontitis (McDevitt et al. 2000), however all other studies have failed to find this association (Table 6). Nevertheless, it has also been reported that patients with the *IL1* composite genotype more often harbored putative periodontal pathogens and have increased counts of these pathogens (Socransky et al. 2000). Interestingly, Laine et al. (2001) reported increased frequency of the *R*-alleles of the *IL1A*, *IL1B* and *IL1RN* genes in non-smoking patients in whom *P. gingivalis* and *A. actinomycetemcomitans* could not be detected. These latter results suggest that *IL1* gene polymorphisms may play a role in the absence of other (putative) risk factors, in contrast to other reports as mentioned above (Meisel et al. 2002b, 2003, 2004). Studies among Chinese-Americans and African-Americans have not resulted in interpretable findings (Table 6) because the *IL1* composite genotype was hardly present in these ethnic populations (Armitage et al. 2000, Walker et al. 2000). In subjects of Southern America the carriage rate of the *IL1* composite genotype (up to 25%) was somewhat lower than that reported for Europeans and Northern American study subjects (up to 48%), and no associations with periodontitis have been found.

Several longitudinal studies on *IL1* polymorphisms have been performed (Table 6). From these studies it may be possible to assess whether a given genotype can be considered a true risk factor. For example, it was reported among periodontitis patients in maintenance over 5–14 years, that the *IL1* composite genotype increased the risk of tooth loss by 2.7-fold (McGuire & Nunn 1999). The *IL1* composite genotype in combination with heavy smoking increased the risk of tooth loss by 7.7-fold (McGuire & Nunn 1999). In an Australian study 295 gingivitis and moderate periodontitis subjects were followed for 5 years and the *IL1* composite genotype was determined (Cullinan et al. 2001); the investigators reported that among non-smoking subjects >50 years, those that were *IL1* composite genotype positive, had deeper probing depths than *IL1* composite genotype negative subjects. Furthermore, a significant interaction was found between *IL1* composite genotype positivity and age, smoking and the presence of *P. gingivalis*, which suggests that the *IL1* composite genotype is a contributory but non-essential risk factor (Cullinan et al. 2001).

In summary, for the global population, polymorphisms in the *IL1* gene cluster cannot be regarded as (putative) risk factors for periodontitis or severity of periodontal destruction. For Caucasian patients with chronic periodontitis the role of the *IL1* composite genotype seems to hold some promise; however, to date no clear evidence has emerged, and there are currently too many conflicting and negative results. Large cohort studies of homogeneous composition should be initiated in which all

Table 7. Carriage rate of the *Rare* (*R*)-allele for polymorphisms in the *TNFA* gene, mainly in case–control studies, and association with periodontitis

TNFA gene polymorphism	Reference	Ethnicity of subjects	Patients			Controls		Associated with periodontitis	Associated with severity of periodontitis
			Diagnosis of cases	*n*	*R*-allele carriage (%)	*n*	*R*-allele carriage (%)		
− 1031	Soga et al. (2003)	Japanese	AP	64	36	64	22	+	n.t.
	Endo et al. (2001)	Japanese	G-EOP	46	30	104	25	–	n.t.
− 863	Soga et al. (2003)	Japanese	AP	64	39	64	25	+	n.t.
− 367	Craandijk et al. (2002)*	Mixed	CP	90	2	264	2	–	–
− 308	Galbraith et al. (1998)	Caucasian	AP	32	28	32	24	–	–
	Galbraith et al. (1999)	Caucasian	AP	40	20	45	24	+	–
	Craandijk et al. (2002)*	Mixed	CP	90	27	264	29	–	–
	Fassmann et al. (2003)	Caucasian	CP	132	21	114	24	–	–
	Folwaczny et al. (2004d)	Caucasian	CP	81	36	80	28	–	n.t.
	Endo et al. (2001)	Japanese	G-EOP	46	4	104	4	–	n.t.
	Soga et al. (2003)	Japanese	AP	64	2	64	3	–	n.t.
	D'Aiuto et al. (2004)†	Mixed	CP	94	25			n.t.	− (+‡)
− 238	Galbraith et al. (1998)	Caucasian	AP	32	6	32	6	–	–
	Craandijk et al. (2002)*	Mixed	CP	90	6	264	6	–	–
	Endo et al. (2001)	Japanese	G-EOP	46	2	104	5	–	n.t.
	Soga et al. (2003)	Japanese	AP	64	0	64	3	–	n.t.
+489	Craandijk et al. (2002)*	Mixed	CP	90	24	264	19	–	–

Abbreviations and symbols as in Table 2.
*Eighty-one per cent of study population is of Caucasian heritage.
†Mixed population: 65% Caucasian; 20% Asian; 15% African or Afro-Caribbean.
‡Elevated levels of IL-6 in serum associated with *R*-allele.

of the currently accepted non-genetic (putative) risk factors are included. Multivariate analyses should be employed to estimate relative contributions of all factors.

Epidemiological findings for TNFA gene polymorphisms

The *TNFA* gene is located on chromosome 6 within the major histocompatibility complex (MHC) gene cluster. Several case–control studies in both Caucasians and non-Caucasians have investigated genetic polymorphisms in the *TNFA* gene as putative risk factors for periodontitis. SNPs in the gene encoding TNF-α are mainly studied in the promoter region at positions − 1031, − 863, − 367, − 308, − 238, but also in the coding region in the first intron at position +489. The results of these studies are summarized in Table 7.

Similar to findings for genes of the *IL1* cluster, differences for the carriage rate of the *R*-alleles between Caucasians and other ethnic populations were apparent; at position − 308 the *R*-allele carriage rate for Caucasians varied between 20% and 3%, while this was 2–3% for Japanese (Table 7). For the *TNFA* − 238 the frequencies of *R*-alleles were comparable between both ethnic populations (< 10%) (Table 7). The carriage rates of the *R*-alleles at positions − 367 and − 238 were < 10%, making them less likely to be associated with periodontitis; indeed no associations have been found with periodontitis for these SNPs (Galbraith et al. 1998, Craandijk et al. 2002, Soga et al. 2003).

Among Japanese, associations with periodontitis have been observed for the SNPs *TNFA* − 1031 and − 863 (Soga et al. 2003); these polymorphisms have not been tested in Caucasians (Table 7). Among Caucasians, the only association of a *TNFA* polymorphism was observed at position − 308 by Galbraith et al. (1999), and this was not corroborated by other studies with Caucasians in the study population. Among families with a high prevalence of EOP, the *TNFA* − 308 gene polymorphisms have also been investigated, but were found not to be associated with EOP (Shapira et al. 2001). Another marker in the *TNFA* gene was investigated in relation to susceptibility for aggressive periodontitis. This marker was based on a variable number of micro-satellite repeats, but was not found to be associated with generalized juvenile periodontitis (GJP) (Kinane et al. 1999).

Investigations into the severity of periodontitis in relation to any of the *TNFA R*-alleles did not reveal a positive association. The carriage of the *R*-allele at nucleotide positions − 308 and − 238 revealed no association between the percent of teeth with ⩾50% bone loss (Craandijk et al. 2002). Moreover, the carriage rates of the *R*-alleles at nucleotide positions − 376, − 308, − 238 and +489 were not different between patients with moderate or severe periodontitis. Others reported also a lack of association of *TNFA* genetic polymorphisms with the severity of periodontitis (Kornman et al. 1997, Galbraith et al. 1998).

Based on the available literature to date, there is very limited data to support associations between any of the reported *TNFA* gene variations and periodontitis. *TNFA* − 1031 and − 863 may have promise, but they have only been tested in one study among Japanese subjects. More studies are needed to address *TNFA* polymorphisms and these studies should also involve investigations into other genetic polymorphisms in genes like *IL1*, for possible gene–gene interactions that may play a role in the complex pathogenesis of periodontitis.

Fcgamma receptor (*FcγR*) gene polymorphisms

Leukocytes from both the myeloid and lymphoid lineages express receptors (FcγR) for the constant (Fc) region of immunoglobulin G molecules (van der Pol & van de Winkel 1998, van Sorge et al. 2003). Indeed, FcγR are found on a wide variety of immune cells in the

periodontal tissues (Yuan et al. 1999). FcγRs are likely to play a role in the pathogenesis of periodontitis as a bridge between the cellular and humoral branches of the immune system. Microorganisms and bacterial antigens, opsonized with antibody, can be phagocytosed via FcγR on neutrophils or internalized via FcγR by a variety of antigen-presenting cells (APC), including monocytes, macrophages and B cells. T cells and natural killer (NK) cells may become activated, when IgG-opsonized bacteria are bound to these cells via FcγR; a variety of cytokines and chemokines may also be released (van der Pol & van de Winkel 1998, van Sorge et al. 2003). When one or several of the FcγR-mediated leukocyte functions are compromised or exaggerated due to genetic polymorphisms in the FcγR genes, it is conceivable that the susceptibility to and/or severity of periodontitis is affected. This concept was proposed almost a decade ago (Wilson & Kalmar 1996).

The leukocyte *FcγR* genes are found on chromosome 1 and encode three main receptor classes: FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16). These classes are further subdivided into subclasses: FcγRIa and b, FcγRIIa, b and c, and FcγRIIIa and b. FcγRIIa is found on all granulocytes, on APC, platelets, endothelial cells and a subset of T cells. FcγRIIIa is present on monocytes and macrophages, natural killer (NK) cells and a subset of T cells. The FcγRIIIb is the most abundantly expressed IgG receptor on neutrophils.

Structural and functional differences in FcγRIIa, IIIa and b have been described (van der Pol & van de Winkel 1998, van Sorge et al. 2003). G to A transition polymorphisms in the *FcγRIIa* gene result in the substitution of histidine (H) (N-allele) for arginine (R) (R-allele) at amino acid position 131 of the receptor. *FcγRIIa*-H131 binds IgG2 immune complexes efficiently, whereas the *FcγRIIa*-R131 allotype cannot mediate this interaction (Warmerdam et al. 1991). The G to T transition polymorphism in the *FcγRIIIa* gene, results in an amino acid 158-valine (V) (N-allele) substitution for 158-phenylalanine (F) (R-allele). The FcγRIIIa-V158 has a higher affinity for IgG1 and 3 than *FcγRIIIa*-F158. Moreover, FcγRIIIa-V158 can bind IgG4, while FcγRIIIa-F158 is unable to do so. A bi-allelic polymorphism in the *FcγRIIIb* gene underlies the FcγRIIIb-neutrophil antigen (NA) 1 or NA2 allotype (the *N*- or *R*-allele respectively). This is caused by 4 amino acid substitutions in the Fc-binding region resulting in differences in glycosylation. The NA2 type binds less efficiently human IgG1 and IgG3 immune complexes than FcγRIIIb-NA1.

Several studies have investigated the *FcγRIIa* polymorphisms in relation to periodontitis (Table 8). In Caucasians and African-Americans, the carriage rate of the *R*-allele is relatively high: 63–77% (Colombo et al. 1998, Meisel et al. 2001, Fu et al. 2002, Loos et al. 2003, Yamamoto et al. 2004). In Japanese the carriage rate is lower: 39–50% (Table 8). In Japanese and African-Americans, the *FcγRIIa* polymorphisms are not associated with periodontitis or with the severity of the disease. However, in Caucasians two studies out of four showed an association, with the *N*-allele rather than the expected *R*-allele. A weak relationship with aggressive periodontitis was observed for the *FcγRIIa N*-allele (Loos et al. 2003). Moreover, periodontitis patients (aggressive and chronic periodontitis) homozygous for the *N*-allele (H/H131 genotype) have more periodontal bone loss than the other patients carrying one or two *R*-alleles. Recently, Yamamoto et al. (2004) also observed a decreased prevalence of the FcγRIIa *R*-allele among Caucasian periodontitis patients and controls in a large case–control study. Homozygosity for the *N*-allele was significantly more prevalent in periodontitis (Yamamoto et al. 2004).

The carriage rates of the *FcγRIIIa* gene are presented in Table 9. Again a lower *R*-allele carriage rate is seen in Japanese than in Caucasians and African-Americans. The *FcγRIIIa N*-allele (V158) was proposed as a putative risk factor for periodontitis, in particular for aggressive periodontitis in a group of Dutch patients (Loos et al. 2003). Also Meisel et al. (2001), in a German population, studied *FcγRIIIa* polymorphisms in relation to periodontitis severity and observed more severe periodontal bone destruction in homozygous *FcγRIIIa N*-allele patients (V/V158). In a Japanese population it was found that the *FcγRIIIa R*-allele (F158) was over-

Table 8. Carriage rate of the *Rare* (*R*)-allele at gene and amino acid position *FcγRIIa* 131, mainly in case–control studies, and association with periodontitis

Reference	Ethnicity of subjects	Patients			Controls		Associated with periodontitis	Associated with severity of periodontitis
		Diagnosis of cases	*n*	*R*-allele carriage (%)	*n*	*R*-allele carriage (%)		
Colombo et al. (1998)*	Caucasian	CP	54	76	24	71	–	–
Meisel et al. (2001)	Caucasian	CP	154	72			n.t.	–
Loos et al. (2003)	Caucasian	AgP and CP	68	65	61	75	– (+†)	– (+‡)
Yamamoto et al. (2004)	Caucasian	CP	213	63	209	75	– (+§)	– (+‡)
Kobayashi et al. (1997)	Japanese	AP	100	44	105	40	–	–
Kobayashi et al. (2000)	Japanese	AP	83	46	104	39	–	–
Kobayashi et al. (2000)	Japanese	G-EOP	38	50	104	39	–	–
Kobayashi et al. (2001)	Japanese	AP	89	42	64	42	–	–
Fu et al. (2002)	African-American	L-AgP	48	77	67	67	–	n.t.
Chung et al. (2003)	Taiwanese	G-AP and CP	75	59	48	62	–	n.t.

Abbreviations and symbols as in Table 2.

*Predominantly Caucasian, actual percentage of subjects of non-Caucasian heritage is not provided.

†*N*-allele is associated with AgP.

‡*N*-allele is associated with severity.

§*N*-allele is associated with periodontitis in smokers.

Table 9. Carriage rate of the *Rare* (*R*)-allele at gene and amino acid position *FcγRIIIa* 158, mainly in case–control studies, and association with periodontitis

Reference	Ethnicity of subjects	Patients			Controls		Associated with periodontitis	Associated with severity of periodontitis
		Diagnosis of cases	*n*	*R*-allele carriage (%)	*n*	*R*-allele carriage (%)		
Meisel et al. (2001)	Caucasian	CP	154	56			n.t.	– (+*)
Loos et al. (2003)	Caucasian	AgP and CP	68	77	61	59	– (+†)	–
Sugita et al. (1999)	Japanese	AP	100	42	104	46	–	+‡
Kobayashi et al. (2000)	Japanese	AP	83	43	104	46	–	–
Kobayashi et al. (2000)	Japanese	G-EOP	38	42	104	46	–	–
Kobayashi et al. (2001)	Japanese	AP	89	49	64	39	–	– (+§)
Fu et al. (2002)	African-American	L-AgP	48	58	67	54	–	n.t.

Abbreviations and symbols as in Table 2.
**N*-allele is associated with severity.
†*N*-allele is associated with AgP.
‡Associated with disease recurrence.
§Association of *N*-allele with disease severity, also in combination with *FcγRIIIb R*-allele.

Table 10. Carriage rate of the *Rare* (*R*)-allele (NA2) at gene *FcγRIIIb*, mainly in case–control studies, and association with periodontitis

Reference	Ethnicity of subjects	Patients			Controls		Associated with periodontitis	Associated with severity of periodontitis
		Diagnosis of cases	*n*	*R*-allele carriage (%)	*n*	*R*-allele carriage (%)		
Colombo et al. (1998)*	Caucasian	CP	54	89	24	75	–	–
Meisel et al. (2001)	Caucasian	CP	154	89			n.t.	–
Loos et al. (2003)	Caucasian	AgP and CP	68	88	61	92	–	–
Kobayashi et al. (1997)	Japanese	AP	100	63	105	64	–	+†
Kobayashi et al. (2000)	Japanese	AP	83	64	104	64	–	n.t.
Kobayashi et al. (2000)	Japanese	G-EOP	38	83	104	64	+ (+‡)	n.t.
Kobayashi et al. (2001)	Japanese	AP	89	62	64	56	–	– (+§)
Fu et al. (2002)	African-American	L-AgP	48	77	67	64	+	n.t.
Chung et al. (2003)	Taiwanese	G-AP and CP	75	63	48	45	–	n.t.

Abbreviations and symbols as in Table 2.
*Predominantly Caucasian, actual percentage of subjects of non-Caucasian heritage is not provided.
†Associated with disease recurrence.
‡Also in combination with *FcγRIIIa R*-allele.
§Association with severity in combination with *FcγRIIIa N*-allele.

represented in patients with periodontal disease recurrence (Sugita et al. 1999). In contrast, another Japanese study showed that the *FcγRIIIa N*-allele was over-represented in patients with severe periodontitis *versus* subjects with moderate disease (Kobayashi et al. 2001). It is apparent that there are conflicting results and comparisons between the different studies are difficult as the prevalences of *FcγR* genotypes are different among subjects of different ethnic background.

The studies that have investigated the *FcγRIIIb* polymorphisms in relation to periodontitis are summarized in Table 10. In Japanese patients, the *FcγRIIIb R*-allele (NA2) was associated with generalized (G)-EOP (Kobayashi et al. 2000) and was found more often in adult patients with disease recurrence (Kobayashi et al. 1997). The combined carriage of both the *R*-allele of the *FcγRIIIb* gene and the *R*-allele of the *FcγRIIIa* gene was more frequently detected in Japanese G-EOP over healthy Japanese controls (Kobayashi et al. 2000). In African-Americans, an association between the *FcγRIIIb* and periodontitis has been found. The carriage rate of the *FcγRIIIb R*-allele in Caucasians was relatively high (>75%) and no associations with periodontitis have been found.

The possibility that genes encoding for Fcγ receptors are associated with periodontitis in different ethnic groups seems promising. However, to date no clear and convincing data are present to definitively assign one or more of the *FcγR* gene polymorphisms as true risk factors for periodontitis. Further research is needed in larger groups of subjects from different global populations to confirm the current observations. Furthermore, functional studies among subjects with different FcγR genotypes need to be undertaken to investigate the corresponding phenotypes and unravel the role of the Fcγ receptors in the pathogenesis of periodontitis.

Gene polymorphisms in the innate immunity receptors

The innate immune response is the first line of defense in infectious diseases. The host is challenged to detect the pathogen and to mount a rapid defensive response. The innate immune system recognizes pathogen-associated molecular patterns (PAMPs) that are expressed on microorganisms, but not on host cells. Extra- and intracellular receptors like CD14, CARD15 and Toll-like receptors (TLRs) recognize PAMPs of Gram-positive and Gram-negative bacteria and mediate the production of

cytokines necessary for further development of effective immunity. Both TLR2 and TLR4 use CD14 as a co-receptor.

CD14 gene polymorphisms

The *R*-allele in the promoter region of *CD14* at position −260 (−159) enhances the transcriptional activity of the gene (Hubacek et al. 1999). Individuals homozygous for the *R*-allele have increased serum levels of soluble (s) CD14 and an increased density of CD14 in monocytes (Hubacek et al. 1999). The *CD14* −260 SNP has previously been associated of increased risk with myocardial infarction (Hubacek et al. 1999) and Crohn's disease (Klein et al. 2002). Furthermore, increased serum levels of sCD14 have been associated with periodontitis (Hayashi et al. 1999).

Two studies with Caucasian subjects investigated the *CD14* −260 polymorphism in chronic periodontitis (Table 11), but did not find associations (Holla et al. 2002a, Folwaczny et al. 2004a). However, after stratification of the cohort according to gender, it was found that the *CD14* −260 *N*-allele was more prevalent among females with periodontitis (67%) than among healthy control subjects (44%) (Folwaczny et al. 2004a). In a Japanese study, again no association was found between the *CD14* −260 polymorphism and periodontitis, even after subdivision of the patients into a young (<35 years) and old (⩾35 years) age group (*R*-allele: 68% and 79%, respectively) (Yamazaki et al. 2003). Nevertheless, Holla et al. (2002a, 2002b) found among Caucasians a tendency for an increased frequency of homozygosity of the *R*-allele for *CD14* −260 in patients with severe disease (19.2%) compared with the patients with moderate disease (8.3%) (Table 11). In the Japanese non-smoking population, the *CD14* −260 genotype distribution was different between the younger (<35 years) and older (⩾35 years) periodontitis patients (Yamazaki et al. 2003).

Results for another polymorphism in the *CD14* gene have also been reported (Holla et al. 2002a); a higher frequency of the *N*-allele and the *N/N* genotype of the *CD14* −1359 polymorphism was found in patients with severe periodontal disease than in patients with moderate periodontitis (Table 11). The importance of this finding requires further study.

TLR2 and TLR4 gene polymorphisms

The *TLR2* Arg677Trp and Arg753Gln gene polymorphisms have been reported to abrogate the ability of TLR2 to mediate a response to bacterial cell wall components (Bochud et al. 2003). Two common co-segregating missense polymorphisms of *TLR4*, Asp299Gly and Thr399Ile, affect the extracellular domain of the TLR4 protein, leading to an attenuated efficacy of LPS signalling and a reduced capacity to elicit inflammation (Arbour et al. 2000). The *TLR4* Asp299Gly gene polymorphism has been correlated with hypo-responsiveness to inhaled LPS (Arbour et al. 2000), sepsis and infections caused by Gram-negative bacteria (Agnese et al. 2002). One study has attempted to associate these above named *TLR* polymorphisms with periodontitis (Table 11) (Folwaczny et al. 2004b). However, despite the perceived importance of these functional *TLR* polymorphisms, no relation with periodontitis has been observed (Folwaczny et al. 2004b).

CARD15 gene polymorphisms

The 3020insC and 2104 C>T polymorphisms of the *CARD15 (NOD2)* gene leads to impaired activation of nuclear factor-κ B, resulting in altered transcription of pro-inflammatory cytokine genes and reduced expression of these cytokines (Hugot et al. 2001, Girardin et al. 2003). These polymorphisms are strongly associated with Crohn's disease (Hugot et al. 2001); however, to date, these *CARD15* polymorphisms have not been associated with periodontitis (Table 11) (Laine et al. 2004, Folwaczny et al. 2004c). No role for the *CARD15* 3020insC and 2104 C>T polymorphism was found for periodontitis in Caucasians.

Although genes of the innate immunity processes seem good candidates for their association with periodontitis, investigations have not yielded any

Table 11. Carriage rate of the *Rare* (*R*)-alleles at the *CD14, TLR2, TLR4* and *CARD15* genes, in case–control studies, and association with periodontitis

Gene polymorphism	Reference	Ethnicity of subjects	Patients			Controls		Associated with periodontitis	Associated with severity of periodontitis
			Diagnosis of cases	*n*	*R*-allele carriage (%)	*n*	*R*-allele carriage (%)		
CD14 -260*	Holla et al. (2002a)	Caucasian	CP	135	74	207	70	–	–
	Folwaczny et al. (2004a)	Caucasian	CP	70	66	75	76	−(+*)	–
	Yamazaki et al. (2003)	Japanese	CP	163	75	104	82	−(+†)	–
CD14 −1359	Holla et al. (2002a)	Caucasian	CP	135	43	207	42	–	−(+‡)
TLR2 Arg677Trp	Folwaczny et al. (2004b)	Caucasian	CP	122	0	122	0	–	–
TLR2 Arg753Gln	Folwaczny et al. (2004b)	Caucasian	CP	122	3	122	4	–	–
TLR4 Asp299Gly	Folwaczny et al. (2004b)	Caucasian	CP	122	4	122	3	–	–
	D'Aiuto et al. (2004)§	Mixed	CP	94	12			n.t.	–
TLR4 Thr399Ile	Folwaczny et al. (2004b)	Caucasian	CP	122	4	122	4	–	–
	D'Aiuto et al. (2004)§	Mixed	CP	94	6			n.t.	–
CARD15 3020insC	Folwaczny et al. (2004c)	Caucasian	CP	80	4	122	4	–	–
	Laine et al. (2004)	Caucasian	CP	104	5	97	5	–	n.t.
CARD15 2104 (C–T)	Laine et al. (2004)	Caucasian	CP	104	13	97	10	–	n.t.

Abbreviations and symbols as in Table 2.

*Also known as −159.

†*R*-allele associated with early disease development.

‡Increased severity associated with homozygosity of *R*-allele.

§Mixed population: 65% Caucasian; 20% Asian; 15% African or Afro-Caribbean.

strong indications that they might be associated with this condition.

Vitamin D receptor (*VDR*) gene polymorphisms

Alveolar bone destruction results from the periodontitis disease process. If left untreated, consequences of periodontitis are tooth mobility and eventually tooth exfoliation. Therefore, it is conceivable that mediators of bone metabolism play a role in the pathophysiology of periodontitis. With this is in mind investigators have identified genetic polymorphisms in genes coding for mediators in bone homeostasis, in particular the *VDR* gene. Bone homeostasis mediators are linked to factors affecting bone mineral density and have been related to disorders of bone metabolism, such as osteoporosis and osteo-arthritis (Ralston 1997, Uitterlinden et al. 1997, Ban et al. 2000, Gennari & Brandi 2001, Massart et al. 2001, Spector & MacGregor 2004). Interestingly, genetic polymorphisms in the *VDR* gene have also been associated with infectious diseases, in particular, tuberculosis (Gelder et al. 2000, Wilkinson et al. 2000, Roth et al. 2004). In addition to mediating bone homeostasis, vitamin D and its receptor play a role in phagocytosis by monocytes and affect monocyte differentiation (Rockett et al. 1998, Selvaraj et al. 2004).

Several studies have identified a *VDR* polymorphisms in relation to periodontitis at RFLP positions *Taq-1, Bsm-1* and *Fok-1* (Table 12) (Hennig et al. 1999, Tachi et al. 2001, Yoshihara et al. 2001, Sun et al. 2002, Tachi et al. 2003, Taguchi et al. 2003, de Brito Junior et al. 2004). The studies on the *Taq-1* and *Bsm-1* SNPs of the *VDR* gene have found some associations with periodontitis, however not unconditionally (Table 12). The carriage rate of the *R*-allele ranges between 12% and 66% across different ethnic populations; among Brazilians it was in the higher range (45–66%) and in Japanese the lower rate (5–12%). In the study by Hennig et al. (1999) the carriage rate of the *R*-allele ranged between 32% and 37%. Nevertheless, in five case–control studies an association of the *R*-allele with several forms of periodontitis have been observed (Table 12) (Hennig et al. 1999, Tachi et al. 2001, Yoshihara et al. 2001, Sun et al. 2002, de Brito Junior et al. 2004), while in one Japanese study an association with the *N*-allele has been found (Tachi et al. 2003). The apparent discrepancy can currently not be explained; however, it may relate to different gene–environment interactions affecting different ethnic populations and/or it is related to differences in the type of periodontitis being investigated. Moreover, we cannot exclude that there is a lack of consistency in ''case definition'' for each disease type between studies.

The *VDR* gene is an interesting candidate gene for its association with periodontitis, because it affects both bone metabolism and immune functions. Moreover some encouraging results have been found for different ethnic populations. Further studies should be engaged to confirm the current preliminary data.

IL-10 gene polymorphisms

The gene encoding IL-10 is located on chromosome 1, in a cluster with closely related interleukin genes, including *IL-19*, *IL-20* and *IL-24*. IL-10 is produced by monocytes/macrophages and T cells and plays a role in the regulation of pro-inflammatory cytokines such as IL-1 and TNF-α In particular, IL-10 is considered an anti-inflammatory cytokine, down-regulating the pro-inflammatory immune response of the monocyte/macrophage and stimulating the production of protective antibodies (Rousset et al. 1992, de Waal Malefyt et al. 1993). However, it has also been suggested that IL-10 can stimulate the generation of auto-antibodies (Mosmann 1994, Lalani et al. 1997). As a matter of fact, auto-antibodies may play a role in periodontitis (Afar et al. 1992, Berglundh et al. 2002). Functional disturbance in the *IL10* gene due to genetic polymorphisms could be detrimental to host tissues and could be linked to periodontal disease susceptibility. The *IL10* SNPS have been associated with altered IL-10 production (Turner et al. 1997, Crawley et al. 1999, Koss et al. 2000). *IL10* genetic polymorphisms have been associated with systemic lupus erythematosus and rheumatoid arthritis (Llorente et al. 1994, Hagiwara et al. 1996, Isomaki et al. 1996, Lazarus et al. 1997, Mongan et al. 1997, Chong et al. 2004).

IL10 gene microsatellite markers have been investigated in relation to aggressive periodontitis; 77 Caucasian patients with G-EOP were included and matched with a control population

Table 12. Carriage of the Rare (*R*)-allele at the gene for the vitamin D receptor (*VDR*) at position *Taq-1* or *Fok-1* polymorphism in case–control studies and association with periodontitis

VDR polymorphism	Reference	Ethnicity of subjects	Patients			Controls		Associated with periodontitis	Associated with severity of periodontitis
			Diagnosis of cases	*n*	*R*-allele carriage (%)	*n*	*R*-allele carriage (%)		
Taq-1	Hennig et al. (1999)	Caucasian	EOP	69	57	72	57	– (+*)	n.t.
	Sun et al. (2002)	Chinese	EOP and AP	61	16	39	5	– (+†)	n.t.
	Tachi et al. (2003)	Japanese	CP	74	11	94	23	– (+‡)	n.t.
	de Brito Junior et al. (2004)	Brazilian	CP	69	67	44	45	+	n.t.
Bsm-1	Yoshihara et al. (2001)	Japanese	G-EOP and AP	94	19	55	20	– (+§)	n.t.
	de Brito Junior et al. (2004)	Brazilian	CP	69	86	44	82	– (+¶)	n.t.
Fok-1	Tachi et al. (2003)	Japanese	CP	74	63	94	54	–	n.t.

Abbreviations and symbols as in Table 2.

**R*-allele associated with L-EOP, not with all cases of EOP.

†*R*-allele associated with EOP.

‡The *N*-allele is associated with periodontitis, also when adjusted for smoking and diabetes

§In combination with *FcγRIIIb R*-allele in particular in G-EOP.

¶The Taq-1/Bsm-1 N/N haplotype is associated with periodontitis.

(Kinane et al. 1999). However, no significant differences in frequencies of various *IL10* alleles between patients and periodontally healthy controls were observed. Also in Japanese patients either with G-EOP ($n = 18$) or with adult periodontitis (AP) ($n = 34$), as well as 52 controls, polymorphisms in the promoter region of the *IL10* gene were analysed (Yamazaki et al. 2001); promoter polymorphisms are located at positions −1087 (−1082), −824 (−819) and −597 (−592). Only haplotypes were presented (in the sequence −1087, −824, −597), while no genotype frequency data on the each of the three SNPs separately were reported. Sixty-five per cent of the patients carried the haplotype *RRR* and 35% of the patients carried *RNN*; haplotype carriage rates for the controls were 71% and 29%, respectively. No significant differences for the carriage rates of the haplotypes of the *IL10* gene were seen between patients and controls. Also no significant differences were observed for these latter haplotypes between AP and EOP. Striking was the complete absence of the *N*-allele carriage at position −1087 among the Japanese, in contrast to Caucasians (Table 13), where the *N*-allele is the most occurring genetic variant at position −1087 (Yamazaki et al. 2001, Berglundh et al. 2003).

Table 13 gives a summary of case–control studies investigating genetic polymorphisms at 3 promoter positions (−1087, −824 and −597) in the *IL10* gene. The carriage rate of the *IL10* *R*-alleles is often abundant (>50%), except at position −597 in Caucasians. For the latter polymorphism a difference in *R*-allele carriage rate between German Caucasians and a mixed ethnic study population was seen (Gonzales et al. 2002, Scarel-Caminaga et al. 2004); the study by Scarel-Caminaga et al. (2004) showed a higher carriage rate of the *R*-allele at position −597 among periodontitis patients in comparison to controls: 72% *versus* 51%, in a mixed ethnic population, 77% of which was Caucasian, recruited in Brazil. On the other hand, the study by Gonzales et al. (2002) showed the *IL10* −597 *R*-allele carriage rate to be 12% for patients *versus* 29% for controls; this was not significantly different due to the low number of subject recruited in the study. At this point these contradictory results between Scarel-Caminaga et al. (2004) and Gonzales et al. (2002) cannot be explained, except major differences in patient groups and inclusion of a small number of study subjects, which can lead to severe bias.

The *IL10* −1087 polymorphism may be an interesting polymorphism for future studies. It has been shown in one study (Table 13) that the *N*-allele is more abundant in periodontitis in particular in non-smokers (Berglundh et al. 2003). These observations have led the authors to speculate that the *N*-allele prevalence in periodontitis patients may result in higher levels of auto-antibodies, which may lead to increased periodontal destruction (Berglundh et al. 2003). These observations were not corroborated by the Brazilian study (Scarel-Caminaga et al. 2004); the latter study observed a trend for increased carriage of the *IL10* −1087 *N*-allele among controls.

In summary, a limited number of studies have investigated genetic variations at three positions in the *IL10* promoter region. For all three positions some significant differences in the allele carriage rates between patients and controls have been reported. Further studies on *IL10* as candidate gene seem justified.

Miscellaneous gene polymorphisms

Table 14 lists various other candidate gene polymorphisms that have been studied in relation to periodontitis. These are not discussed as the other candidates above, since mainly negative results have been obtained and/or too few studies are published for a meaningful analysis. However, the table illustrates the variety of candidates and the difficulty in interpreting results; if some positive results are reported, these are often in subgroups or conditionally. Clearly, further studies are needed employing larger patient numbers, which focus on candidate genes that have a proven role in the pathophysiology of periodontitis, where gene polymorphisms result in functional changes or are linked to other gene polymorphisms which in turn are strong markers of inflammatory and/or infectious diseases.

Conclusions and Recommendations

An important problem related to research in the heredity of periodontitis is that, whatever the cause of the disease is, the symptoms are the same; specifically, deepening of the periodontal pocket, loss of attachment and alveolar bone loss. It is likely that overlapping clinical phenotypes exist between different forms of periodontitis. It is important that globally accepted definitions of ''cases'' of chronic, and localized and

Table 13. Carriage of the *Rare* (*R*)-allele at the *IL10* gene at positions −1087, −824 and −597, in case–control studies, and association with periodontitis

IL10 polymorphism	Reference	Ethnicity of subjects	Patients			Controls		Association with periodontitis	Association with severity of periodontitis
			Diagnosis of cases	*n*	*R*-allele carriage (%)	*n*	*R*-allele carriage (%)		
−1087 (−1082)	Scarel-Caminaga et al. (2004)	Mixed*	CP	67	88	43	89	–	n.t.
	Berglundh et al. (2003)	Caucasian	CP	60	60	39	80	− (+†)	n.t.
−824 (−819)	Gonzales et al. (2002)	Caucasian	CP and AP	41	56	21	52	–	n.t.
	Scarel-Caminaga et al. (2004)	Mixed*	CP	67	76	43	51	+	n.t.
−597 (−592)	Gonzales et al. (2002)	Caucasian	CP and AP	41	12	21	29	–	n.t
	Scarel-Caminaga et al. (2004)	Mixed*	CP	67	72	43	51	+	n.t.

*Seventy-seven per cent of population is of Caucasian background.

†*N*-allele associated with periodontitis, in particular non-smoking homozygous *N/N* subjects.

Table 14. Polymorphisms in miscellaneous genes studied in relation to periodontitis and reported association

Polymorphism in gene	Reference	Associated with periodontitis
ACE	Holla et al. (2001a)	– (+*)
CCR5	Folwaczny et al. (2003)	–
ER2	Zhang et al. (2004)	–
ET1	Holla et al. (2001a)	–
FBR	Sahingur et al. (2003)	+†
FcγRIIb	Yasuda et al. (2003)	+
FPR1	Zhang et al. (2003)	– (+‡)
IL2	Scarel-Caminaga et al. (2002)	– (+§)
IL4	Michel et al. (2001)	+
	Scarel-Caminaga et al. (2003)	–
	Kang et al. (2003)	–
	Gonzales et al. (2004)	–
	Pontes et al. (2004)	–
IL6	Trevilatto et al. (2003)	+
	Holla et al. (2004a)	– (+¶)
	D'Aiuto et al. (2004)	– (+ ‖)
INFGR1	Fraser et al. (2003)	– (+**)
LTA	Holla et al. (2001a)	+
	Fassmann et al. (2003)	– (+††)
MMP-1	Holla et al. (2004b)	–
	Itagaki et al. (2004)	–
	de Souza et al. (2003a)	– (+‡‡)
MMP3	Itagaki et al. (2004)	–
MMP9	de Souza et al. (2005)	–
MPO	Meisel et al. (2002a)	– (+§§)
NAT2	Kocher et al. (2002)	– (+¶¶)
	Meisel et al. (2000)	+ (+ ¶¶)
PAI1	Izakovicova Holla et al. (2002)	+
RAGE	Holla et al. (2001b)	+
TGFB	Holla et al. (2002b)	–
	de Souza et al. (2003b)	– (+ ‖‖)
TIMP2	de Souza et al. (2005)	–
TNFR2	Scarel-Caminaga et al. (2004)	+

Symbols as in Table 2.
*In combination with LTA.
†*R*-allele associated with higher serum fibrinogen.
‡Associated with LJP in African-Americans.
§*R*- allele associated with severity.
¶*R*-allele protective.
‖ *R*-allele associated with higher serum levels of IL-6.
***R*-allele in combination with smoking.
††*N*-allele protective in combination with *TNFA* −308.
‡‡*R*-allele associated in non-smokers.
§§*R*-allele protective for females.
¶¶NAT2 slow phenotype associated with severity.
‖‖ *R*-allele possibly small effect in relation to severity.

generalized aggressive forms of periodontitis are used in future studies, to allow valid comparisons to be made between gene polymorphism data from different parts of the world. In the majority of cases, it is likely that the development of periodontitis in an individual depends on the collective presence of a number of environmental risk factors in conjunction with a number of genetic risk factors at a given time point during life. The more genetic risk factors an individual has inherited, the greater the genetic predisposition and the higher the chance of early development of periodontitis. Whenever an individual has inherited a major disease gene mutation, we would expect early development of periodontitis. However, to date, major disease gene mutations have not been identified, which result in the periodontitis phenotype in otherwise systemically healthy individuals. Since the children of patients with chronic periodontitis show a relatively high prevalence of incipient periodontitis, it is likely that some forms of early periodontitis share a common pathogenic pathway with that of chronic periodontitis in adults.

A multitude of polymorphisms in genes, most of which code aspects of the host immune response, have been explored. There are indications that some polymorphisms in the *IL1* gene cluster, the *FcγR* gene cluster and in the genes encoding the VDR and IL-10, may be associated with periodontitis in certain ethnic groups. However, in general, even among studies with subjects of the same ethnic background, no consistent results have been obtained. Often, only by defining small subgroups of individuals or after stratification, researchers have found some significant associations, but the studies appear under-powered for proper interpretation. Moreover, carriage of specific combinations of alleles within a given locus (haplotype analysis) and among various genes (gene–gene interactions), have only been sparsely investigated. Therefore, we conclude that until now no specific genetic risk factor for periodontitis has been identified.

In general, the genetic studies in relation to periodontitis are hampered by population heterogeneity and differences in patient selection and diagnostic criteria. However, it is also possible that inconsistent results may reflect the underlying complexity and heterogeneity of genetic influence in periodontitis. Nevertheless, the heterogeneity in case definitions was one of the major problems encountered in the interpretation of the various studies available in the literature in relation to genetic risk factors for periodontitis.

Another problem encountered in the reviewed literature, was that many studies had investigated putative genetic risk factors without considering other, established risk factors for periodontitis as co-variates. For example, most would agree that in periodontal research, age, gender and smoking, should always be included in multivariate analyses to generate adjusted odds ratios. Further, the vast majority of studies has not considered the infectious component (gene–environment interaction). We recommend strongly that, where possible the bacterial microorganisms or appropriate surrogate measures of bacterial infection should be included as co-variates in the analyses.

Future studies applying the candidate gene approach could be guided by results from genome wide searches or by results from gene expression signa-

tures (Papapanou et al. 2004) or family linkage analyses (Diehl et al. 1999, Li et al. 2004b). Furthermore, these type of studies need to be large scale, in consortium-based approaches, because single studies are greatly underpowered. It is estimated that meaningful results for the candidate gene approach may only be obtained with thousands of patients, since most associations refer to small odds ratio's (range 1.1–1.50) (Ioannidis et al. 2003). Useful reviews and recommendations have been published on the topic of the candidate gene approach for complex diseases (Clayton & McKeigue 2001, Tabor et al. 2002, Colhoun et al. 2003, Ioannidis 2003).

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