Mini review

Genetic polymorphisms of Fc gamma receptors and periodontitis

L Chai[1*], Y-Q Song[2], W K Leung[3]

[1]School of Dentistry, University of Queensland, Australia; [2]Department of Biochemistry, Li Ka Shing Faculty of Medicine and [3]Faculty of Dentistry, The University of Hong Kong, Hong Kong SAR, China

*Correspondence: Dr. L. Chai, School of Dentistry, University of Queensland, 200 Turbot Street, Brisbane QLD 4000, Australia. Tel: +61-7-33658033. E-mail: l.chai@uq.edu.au

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Periodontitis is a complex chronic subgingival plaque induced inflammatory disease influenced by multiple factors including genetic, behavior, and environment. Many genetic association studies have been conducted in periodontology. One of the most extensively investigated gene families is the Fc gamma receptor gene family, which plays a key role in regulating host immune responses to bacteria but the data available of this gene family influence in periodontitis are controversial. This article critically reviews the current understanding and research status of genetic polymorphism studies of Fc gamma receptors and periodontitis and also of other genes involved in the regulatory network of Fc gamma receptors with special reference to their anticipated biological roles. Moreover, some possible future research directions in the related area are discussed.

Human periodontitis is a chronic infectious disease that is characterized by plaque induced destruction of periodontal soft tissue and alveolar bone. The etiology of the disease is unclear but is commonly believed to be bacterial infection interacts with host defense which is modified by a multitude of agents, such as genetic, behavioral, and environmental factors (1). In the past decade, many studies have been carried out to investigate genetic susceptibility to periodontal diseases. In this respect, one of the most extensively studied gene families is that of the Fc gamma receptor (FcγR), which has been proven to be essential in the pathogenesis of periodontal disease. In this review, we summarize current genetic association studies on the FcγR gene family and other genes in its immune network. We hope the review will give readers a general idea of the association between FcγR and periodontitis, as well as the current status of genetic study in periodontology and its future directions.

Periodontitis is a complex disease

A classification system based on genetic involvement puts diseases into three categories: chromosomal, Mendelian, and complex (2). Chromosomal disorders are characterized by gross abnormalities in chromosome number or structure, and often result in preterm death related to developmental abnormalities. Mendelian disorders are caused by a few rare mutations of a single gene or, exceptionally, of more than one gene (3, 4). Mendelian disorders usually display familial patterns of inheritance, including autosomal recessive, autosomal dominant, or X-linked transmission of the disease-related alleles, and there is a direct correlation between genotype and phenotype. It is generally accepted that complex

diseases have a multifactorial pathogenesis and develop as a result of the interplay between several genes or genetic variants and environmental factors (including bacterial infection and smoking), somatic mutations, and epigenetic modifications (5). Thus, inherited genetic variation is not the direct cause of a complex disease but instead mediates the risk of disease development in response to exposure to one or more environmental factors. Therefore the clinical and genetic heterogeneity of such disorders makes the analysis of their exact causes extremely difficult (6) (Figure 1).

Genetic factors can influence the intensity and severity of host responses to bacterial challenge, which may result in various levels of periodontal tissue destruction. As a consequence, different patients might exhibit different levels of immune responses to the same level of infection (7-9). Specifically, different allelic variants can lead to variations in different aspects of host immune responses such as innate immunity, adaptive immunity, and auto-immune reaction (10). Genetic variations may also serve as either protective or risk factors for diseases such as periodontitis (11). For these reasons, periodontitis is considered a complex disease whose phenotype is determined by both genetic make-up and environmental influences on the host bacterial interaction within an individual. Therefore, genetic polymorphism studies of periodontitis need careful design and cautious interpretation (9).

Genetic polymorphism study of complex human diseases

Until the availability of detailed genetic maps thanks to the Human Genome Project, the identification of DNA mutations that caused rare disorders, such as cystic fibrosis and Huntington's disease depended on genetic linkage and positional cloning studies (12-15).

However, such approaches were unsuccessful in identifying loci that contribute to complex diseases. In 1996, Risch and Merikangas suggested that association studies could be more powerful than linkage studies in identifying susceptibility loci (16). Furthermore, some researchers postulated the hypothesis that common variants are the base of common diseases, suggesting that common DNA variation, as opposed to rare mutations, could be responsible for a proportion of common diseases (17-19). Although that hypothesis remains controversial, resources for association studies, such as dense genetic maps of single nucleotide polymorphisms (SNPs) across the human genome, enable investigators to more rapidly identify disease-associated loci that could have a major impact on public health (20). Association studies are currently the focus of most study designs for identifying loci involved in complex diseases such as cardiovascular diseases, diabetes, cancer, and periodontal diseases.

There are two approaches for studying candidate SNPs: direct and indirect. In the direct association study, the proposed causative SNP is genotyped directly. Despite the proven success of the direct approach using non-synonymous (non-synonymous change may either be missense or nonsense, where a missense change in the coding sequence results in a different amino acid, while a nonsense change in the coding sequence results in a premature stop codon) SNPs (21), a major challenge is predicting or determining *a priori* which SNPs are likely to be causative or predictive of the phenotype of interest, in particular, since our current knowledge about the pathogenesis of most complex diseases and SNP functions is limited. Hence, the selection of the candidate SNPs is usually difficult. The indirect approach, on the other hand, is much like a linkage study in that it assays multiple markers while assuming them to be neutral, without assuming the

location of the causative gene or locus (22). It is most often a case-control study on subjects drawn from the general population and uses a measure of allelic association or site correlation (known as linkage disequilibrium, LD) to detect historical recombination. This strategy, however, also has some problems: sample selection reduces statistical power, particularly for rare alleles; haplotypes at multiple loci cannot be resolved, thereby precluding some powerful mapping strategies; and clinical samples are less readily analyzable using stratification by phenotypic differences and environmental factors, which may be critical to understanding disease susceptibility (23).

Among recent developments in genomic research is the genome-wide association study (GWAS), which seems more promising than traditional association studies in identifying molecular pathways of diseases, and in a lesser extent, risk variants of complex diseases since it scans the whole genome for association without any prior assumptions about the biological process, hence can possibly find out those variants would not usually be suspected to be associated based on our current limited knowledge of the biological functions of the genes (24). However, researchers are still debating the usefulness of the GWAS in actually helping to predict individual genetic risk of complex diseases because most of GWASs carried out so far have not identified variants by which we can accurately predict genetic risks since the associated variants found out are common and typically have very small effects on the variability of the traits, hence can explain only a small portion of the heritability (25-27). The majority of effect sizes of risk alleles that have been found so far in GWASs are small: typically with an odds ratio of <1.5, and with many around 1.1 and 1.2, which represent the limit of detection given the experimental sample sizes employed to date. Alternatively, an individual identified gene

variant results to only 10% to 20% more susceptible to a certain disease. Those findings suggested that many GWAS so far may not have sufficient power to discover associations with such small effects (Figure 2) (28). Larger-scale GWASs (sample size of more than 10,000) are thus required (27). Moreover, for most diseases, GWAS results usually indicate a substantial number of variants that generate small increases in disease risk; such variants cannot individually explain much of the genetic variance.

Therefore, a combined strategy such as one using rare and low-frequency variants and structure variants may be required (26, 27). A recent combination approach used in diabetes research may show us a possible effective strategy (29). In that study, the researchers used GWAS to investigate 12,000 common non-synonymous SNPs in patients with type I diabetes and healthy controls. They identified a type I diabetes-associated locus on chromosome 2q24 and subsequently used a newly developed high-throughput sequencing technology to resequence the candidate genes in the associated locus. The group found that multiple rare variants in the "interferon-induced with helicase C domain 1" gene (*IFIH1*) was associated with type I diabetes and implicated involvement of the gene in this disease. These associations explained a substantial portion of disease risk and constituted proof of principle for the genome-wide approach and gene fine mapping in the elucidation of complex diseases (29).

Genetic polymorphism study of periodontitis

In the past decade, many association studies on periodontitis have been reported. However, owing to the complicated nature of the disease and the limitations of the study approaches used, our knowledge of the genetic background of periodontitis is still scant

(30). Most of the published research into genetic polymorphisms in periodontitis focuses on genes that play roles in immunoregulation or metabolism, such as genes for cytokines, cell-surface receptors, chemokines, and enzymes, as well as genes related to antigen recognition. The direct association approach is most commonly used, but ethnic heterogeneity, different clinical classification systems, and other factors such as variations in sample size and control criteria were often not standardized meaning that the diverse results remained difficult to comprehend (9). Among the studied genes, FcγRs are one of the gene families gained much attention since they link the cellular and humoral immunity and play a pivotal role in host versus bacteria response (31). However unlike IL-1 cluster, there are few reviews summarizing the FcγR gene family polymorphisms and periodontitis although genetic studies of FcγRs polymorphisms and periodontitis are numerous. The following sections will focus on research that has been undertaken to study the role of FcγRs and other factors such as IL-1 family and other cytokines that are relevant to FcγRs within and beyond their regulatory network in relation to periodontitis, under the context of genetic polymorphisms.

Fc gamma receptor polymorphisms

Biology of Fc gamma receptors

Fc receptors for immunoglobulin G (IgG), or FcγRs, were identified more than 40 years ago with the observation that IgG antibodies could be directly cytophilic for macrophages when presented on opsonized red blood cells (32). This binding property of IgG antibodies was found to be independent of the antibody's hyper-variable (Fab) region and

required only the constant (Fc) portion of the IgG. Subsequent *in vitro* studies established the role of FcγRs in triggering effector responses such as macrophage phagocytosis, natural killer (NK) cell antibody dependent cell-mediated cytotoxicity, neutrophil activation, and the paradoxical inhibition of B cell activation by IgG immune complexes (33-37). Currently, three different classes of human FcγR family are recognized, encompassing nine genes (CD64: *FcγRIa*, *Ib*, and *Ic*; CD32: *FcγRIIa*, *IIb,* and *IIc*; and CD16: *FcγRIIIa* and *IIIb*), which have been mapped to the long arm of chromosome 1 (1q21 and 1q23-24) (38-41). Whereas FcγRI has a high affinity for the antibody-Fc region, FcγRII and FcγRIII have a low affinity for the Fc region of IgG (42, 43). A new member of the FcγR family, FcγRIV, was recently identified in mice. It is considered to be conserved in all mammalian species and to have intermediate affinity (44-46). Although only single copies of the low-affinity Fc-receptor genes are present in most species, duplications and diversification processes have led to the presence of multiple genes in the human genome (47). The copy number variation of FcγRs is becoming one of important genetic polymorphisms for this gene family that we will discuss later in this review. Unfortunately, most likely owing to their highly homologous sequences, many genome databases list these low-affinity FcγRs not as separate genes but, incorrectly, as allelic version of one gene (39).

Most FcγR subclasses consist of a separate ligand-binding chain, whose extracellular domain contains the IgG-binding region, and signaling chains essential for the initiation of signal transduction. The exception is neutrophil FcγRIIIb, which is attached to the outer layer of the cell membrane via a glycosyl-phosphatidylinositol anchor. Functionally, there are two different FcγR classes: activating and inhibitory

receptors, which transmit their signals via immunoreceptor tyrosine-based activation (ITAM) or immunoreceptor tyrosine-based inhibitory motifs (ITIMs), respectively (48). The general characteristics of human FcγRs are summarized in Table 1. The paired expression of activating and inhibitory molecules on the same cell is the key for the generation of a balanced immune response (48).

Fc gamma receptors and periodontitis

FcγRs are found on a wide variety of immune cells, such as polymorphonuclear granulocytes, lymphocytes, and dentritic cells, in both gingival epithelium and pocket epithelium of periodontal tissues (49). Indeed, strong, specific IgG responses against periodontopathic bacteria have been observed in gingival tissue and gingival crevicular fluid (50). Furthermore, microorganisms and bacterial antigens that have been opsonized with antibody, can be either phagocytosed via FcγRs on neutrophils or internalized via FcγRs by antigen-presenting cells (dendritic cells, monocytes, macrophages, and B cells). As a consequence, T cells and NK cells may become activated; a variety of cytokines and chemokines may also be released (51). Because FcγRs on leukocytes in effect link cellular and humoral branches of the immune system, they can be considered to be an essential component of the host-defense mechanism against bacteria (31). Therefore, any alteration in FcγR expression and function would alter host immune responses against periodontal pathogens and hence susceptibility to periodontal diseases.

Since the recent realization that FcγRIV is a highly conserved member of the FcγR family, researchers have begun refocusing on the affinity of individual Fc receptors for different antibody isotypes (52). One hypothesis is that the low-affinity inhibitory

FcγRIIb differentially regulates each activating Fc receptor type, depending on the antibody isotype it is regulated by (39). The *in vivo* activity of an IgG antibody, therefore, can be predicted on the basis of its activation/inhibition ratio, which in turn is influenced by several factors. Inflammatory mediators, including interferon (IFN-) γ, complement component 5a (C5a), and Th-1 cytokines such as interleukin (IL-) 1β and tumor necrosis factor (TNF-) α can upregulate activating Fc receptors, while simultaneously decreasing the level of FcγRIIb expression (52-54). The expression of FcγRI can be upregulated by IFN-γ resulting in elevated mRNA expression of TNF-α, granulocyte macrophage colony stimulating factor (GM-CSF), IL-3, and IL-13 (55). In contrast, Th-2 cytokines such as IL-4, IL-5, IL-10, IL-13, or transforming growth factor (TGF-) β upregulate expression of inhibitory Fc receptors and downregulate that of activating Fc receptors on innate immune effector cells (53, 55-58). It should be noted, however, that cytokine-mediated regulation of FcγR expression is cell type-specific. For example, IL-4 upregulates FcγRIIb expression on myeloid cells, but downregulates FcγRIIb expression on activated B cells (59). Table 2 lists members the FcγR regulatory network and their relation with FcγRs (except FcγRIV).

Fc gamma receptor polymorphisms

Functional bi-allelic polymorphisms have been identified for four FcγR subclasses: FcγRIIa, FcγRIIc, FcγRIIIa, and FcγRIIIb (60-64). FcγRIIa contains either an arginine (-R131) or a histidine (-H131) at amino acid position 131 in the second extracellular immnunoglobulin-like domain (RefSNP: rs1801274) (65, 66). Depending on the amino acid, the receptor affinity for IgG2 is strongly affected (67). For example, FcγRIIa-

H/H131 neutrophils internalize human IgG2-opsonized bacteria more efficiently than FcγRIIa-R/R131 neutrophils (68). Several studies have shown that allelic polymorphisms in the first extracellular domain (EC1) of FcγRIIc corresponding to amino acid position 13 (EC1-13) with either a CAG or a TAG can possibly determine the expression and function of FcγRIIc on normal human NK cells because CAG is a codon for Gln while TAG is a stop codon, hence results in either a functional open reading frame or a null allele (60, 61). Further, receptor affinity for both monomeric and immune-complexed IgG1and IgG3 is higher for the FcγRIIIa-158V allotype than the FcγRIIIa-158F allotype (rs396991) (69). Neutrophil-specific FcγRIIIb polymorphisms are characterized by their reactivity to anti-FcR III monoclonal antibodies and alloantisera that recognize determinants of the biallelic neutrophil antigen (NA) system. Receptors that react with only monocolonal antibody Gran 11 and anti-NA1 alloantibodies are regarded as NA1NA1, while receptors that react with only anti-NA2 alloantibodies are NA2NA2 and the remainder, which can react with both anti-NA1 and anti-NA2 alloantibodies, are NA1NA2 (62, 70). The NA1-NA2 polymorphisms caused by five bases changes in codons 36, 38, 65, 82, and 106 lead to four predicted amino acid substitutions within the first extracellular immunoglobulin-like domain (70). As a result, NA1 has only four potential N-linked glycosylation sites as compared with six in NA2 FcγRIIIb (70). Neutrophils from FcγRIIIb-NA2 individuals bind IgG1 or IgG3 less efficiently than neutrophils from individuals with FcγRIIIb-NA1 (68). *In vitro* findings have suggested that inter-individual differences in the efficacy of FcγR-mediated effector functions depend on FcγR polymorphisms. Figure 3 illustrates the function of FcγRs and summarises most of their related polymorphism studies.

Apart from SNPs, Fcγ receptor genes exhibit variation in their copy numbers as well. Copy number variation has been demonstrated for *FCGR3B*, *FCGR2C* and *FCGR3A* genes, but not for *FCGR2A* or *FCGR2B* (71). Copy number variation in *FCGR3B* has been shown to be associated with surface expression of FcγIIIb in neutrophils. In addition, neutrophils isolated from donors with more than two gene copies displayed enhanced IgG-induced effector responses as well as increased cell adherence in IgG-coated surfaces compared with those from donors with less than two (72). The copy number variation of *FCGR3B* has been reported to be associated with several chronic inflammatory diseases such as SLE (72), rheumatoid arthritis (73) and immune-mediated glomerulonephritis (74). *FCGR2C* copy number variation is found to be associated with idiopathic thrombocytopenic purpura (75). The same study also reported that NK cells from individuals with two or three copies of *FCGR3A* seem to express higher levels of receptor and exhibit greater antibody-dependent killing capacity than those from individuals with one copy of the gene (75). It should be noticed that although a number of studies have made use of well validated complementary techniques for the assessment of copy number variation, there is controversy on the accuracy and sensitivity of some of these techniques, as they are still at an early stage of technical development.

Fc gamma receptor polymorphisms and periodontitis

Most studies on the association between genetic polymorphisms of FcγRs and periodontitis are based on the bi-allelic polymorphisms mentioned above. Studied groups have come from Caucasian, African-American, Japanese, and Chinese populations. Different definitions of periodontitis that have been used include early onset

periodontitis, adult periodontitis, aggressive periodontitis, chronic periodontitis and recurrent periodontitis (31, 76-88) (Table 3). Unsurprisingly, the differing populations, periodontitis types, and study designs have led to mixed conclusions (89). Apart from most of the association studies trying to establish confirmed association between those single FcγR polymorphism mentioned above and periodontitis, some researchers tried to use different strategies to look for associated variations. Chai et al. has screened 103 SNPs in FcγRs and reported a novel SNP (rs445509) in FcγRIIIa that may associated with chronic periodontitis in Chinese (76). Nicu et al. have investigated the function of FcγR genetic variants on host against periodontopathogenic bacteria. They has reported periodontitis patients with FcγRIIa H/H-131 genotype seemed suffering more bone loss comparing to H/R or R/R genotype periodontitis patients and their PMNs showed higher reactivity in response to periodontopathogenic bacteria than those of patients with other genotypes (89-91). So far there is no study about copy number variation of FcγRs and periodontitis can be found yet.

Although researchers have shown some evidence that FcγRIIa and FcγRIIIa polymorphisms as well as FcγRIIIb polymorphisms (except for chronic adult periodontitis) may be associated with periodontitis, more studies on various populations are needed to confirm if these conclusions can be extrapolated to the general population. Moreover, it should be noticed that FcγRIIb polymorphisms may also play an important role in the pathogenesis of periodontitis, because there are large numbers of FcγRII-bearing B lymphocytes in periodontal lesions and FcγRIIb is so far the only known inhibitory receptor in the FcγR family that is pivotal in the regulation of B cell activation.

Indeed, an association between FcγRIIb-232T and aggressive periodontitis has been shown in Japanese subjects (89, 91).

Genetic polymorphisms within the Fc gamma receptor regulatory network

As shown in Table 2, the members of the FcγR regulatory network can be categorized as upregulatory factors such as IL-1β, TNF-α, IFN-γ, IL-13, C5, IL-3 and GM-CSF; downregulatory factors such as IL-10, TGF-β and IL4; and cytokines that have both functions (Figure 3). Compared with FcγRs, cytokines of their regulatory network, such as IL-1 and TNF-α, have received more attention in terms of the number of studies on polymorphisms and periodontitis susceptibility. Nevertheless, some members of the regulatory network have been neglected, especially in periodontal susceptibility studies. The following sections will discuss genetic polymorphisms within the FcγR regulatory network in detail.

Upregualtory factors

Interleukin-1 family

The biological activity, molecular biology, and clinical relevance of the IL-1 family have been studied extensively. IL-1 is a potent pro-inflammatory cytokine that is released by macrophages, platelets, and endothelial cells. The gene encoding this cytokine lies on chromosome 2q13-21 (92-94). In 1997, Kornman *et al* reported an association between polymorphisms in the genes encoding IL-1α (-889) (rs1800587) and IL-1β (Y3953) (rs1143634) (termed the "composite genotype") and an increased severity of periodontitis (95). This initial study has been highly influential in arousing interest in gene

polymorphisms and periodontitis. The IL-1 family has become the most studied in the search for genetic associations with periodontitis and can serve as a useful example for considering the strengths and limitations of using gene polymorphisms in disease association studies in periodontitis.

On the basis of numerous studies of IL-1 composite genotypes and periodontitis, Kinane *et al* (10) summarized current understanding of the association between IL-1 family genotypes and periodontitis. The overall findings are as follows: a) the IL-1 composite genotype appears irrelevant in aggressive periodontitis; b) such composite genotype may be in linkage disequilibrium with the gene contributing to susceptibility to chronic periodontitis; c) the composite polymorphisms may be part of several involved in the genetic risk for chronic periodontitis; d) the polymorphism is only a useful marker in defined population (96, 97); e) comfirmation of the functional significance of this gene polymorphism remains to be established; f) clinical utilization of the composite polymorphisms for risk assessment and prognostic determination is premature. A recent meta-analysis supports these opinions by showing a statistically significant association between IL-1 cluster polymorphisms and chronic periodontitis (98). The same metaanalysis also found a weak positive association with IL-1β (-511) (rs16944) (98).

Tumor necrosis factor

TNF is a pro-inflammatory cytokine that possesses a wide range of immunoregulatory functions. It has the potential to stimulate the production of secondary mediators, including chemokines or cyclooxygenase products, which consequently amplify the degree of inflammation (99, 100). The TNF gene is located on chromosome 6 within the

major histocompatibility complex, in the 6p21.3 Class III human leukocyte antigen zone (101). Research on some SNPs such as -1031T/C (rs1799964), -863C/A (rs1800630), -857C/T (rs1799724), and -308G/A (rs1800629) in the promoter region of this gene has revealed conflicting findings for their association with periodontitis (102-110). Meta-analysis of studies done so far on -308G/A could not establish an association between the polymorphism and susceptibility to chronic periodontitis (98).

Miscellaneous factors

Studies on IFN-γ -874T/A (rs2430561) and chronic periodontitis have shown mostly negative results (111-113). A study on the IL-13 promoter polymorphisms -1112C/T (rs1800925) and -1512A/C (rs1881457) in aggressive periodontitis also did not show significant results (114). Other inflammatory mediators such as C5 rs17611 have been found to be associated with severe chronic periodontitis in the Chinese population (115). Additionally, C5 1632C/T (rs25681) and 2404A/G (rs17611) have been found to be associated with bronchial asthma (116), rs17611 and rs2300929 with liver fibrogenesis (117).

Downregulatory factors

Interleukin-10

IL-10 stimulates the production of protective antibodies and downregulates proinflammatory cytokines produced by monocytes (118-120). The gene encoding IL-10 has been mapped to chromosome 1q31-32 (121). Three promoter SNPs have been described: -1087G/A (rs1800896), -819C/T (rs1800871), and -592C/A (rs1800872) (122,

123). These three loci exhibit strong LD (124). There is some evidence of association of such polymorphism with periodontitis, but only in particular populations (125-128). Microsatellite polymorphisms have been identified in the 5'-flanking region of the gene, but no association with periodontitis has been established (108, 129).

Transforming growth factor-β1

TGF-β1 is released during tissue injury and by inflammatory cells exposed to bacteria and their products (130). It has both therapeutic and pathologic potential (131). The gene is located on chromosome 19q13.1 (132), and SNP -509C/T (rs1800469) has been reported to be associated with periodontitis in Brazilian Caucasians but not Czech Caucasians (133, 134).

Interleukin-4

IL-4 can rescue B lymphocytes from apoptosis and enhance their survival, thus playing a role in promoting B cell mediated autoimmunity (111). It is also a potent downregulator of macrophage function (135, 136). The gene has been mapped to chromosome 5q31.1 (137), with a promoter SNP at position -590 (rs2243250) and a 70-bp variable-number tandem repeat polymorphism at intron 2 (11). Case-control reports relating to aggressive periodontitis and chronic periodontitis susceptibility and severity across several populations did not find a connection between these polymorphisms and periodontitis (138-142).

Other regulatory members

So far, no study on IL-3 and IL-5 polymorphisms in periodontal diseases has been reported. However, reports on IL-3 +79T/C (rs40401) in association with asthma and atopy (143), IL-3 -16T/C, -131T/C in association with rheumatoid arthritis (144), and IL-5 rs2522411 and -703C/T in association with atopic dermatitis (145, 146) have been published. GM-CSF 545G/A (rs2069616), 3606T/C (rs25881), and 3928C/T (rs25882) have also been found to be associated with atopic diseases (147). Whether any of these genetic polymorphisms are related to periodontitis still need further investigation.

Limitations and future directions

Other than genetic polymorphism studies, large-scale genomic screening and large scale population investigations in periodontal research, such as multi-community screening, are rare. The paucity of research may be due to the complex natural course of periodontitis, lack of a robust classification system, difficulties in searching matched controls, or other factors (30). Most of the studies about FcγR polymorphisms and periodontitis have focused on single or several variations of the candidate genes in a certain population (e.g. studies listed in Table 3), and have provided vast quantities of diverse data that are difficult to interpret and lead to general conclusions. Even for the most extensively studied variations in the IL-1 cluster, meta-analysis can only give a positive conclusion in Caucasians (10, 98). Moreover, the number of studies providing thorough data (e.g. allele type, genotype, haplotype) together with Hardy-Weinberg equilibrium and minor allele frequencies, is small.

Although the FcγR genetic polymorphism studies related to periodontal diseases in the past decade have given us some evidence that FcγR genetic variants can modify host immune responses and lead to different phenotypes of periodontal disease, it is too early to draw any conclusions. With the completion of the Human Genome Project and the availability of cutting-edge technology, the application of genetic information and technology to the diagnosis and treatment of periodontitis is conceptually compelling. Nonetheless, it is important to maintain a realistic perspective of the clinical utility of genetic information (148, 149). In the future, researchers should also be cautious of numerous weak associations that may turn out to be spurious at repeated testing (150). It is not enough that only the racial and ethnic backgrounds of the subjects are taken into account; studies must have sufficient numbers of cases and controls, with the controls carefully chosen to make the association between polymorphisms and periodontitis much clearer. The choice of candidate genes must also be justifiable and the data clearly presented to show the range of effect and risk attributable to the gene variation. In many currently published genetic association studies, the reported associated SNPs show no obvious function, thus providing few clues on pathogenesis. Recent developments in high-throughput target resequencing can overcome this limitation by searching for variants in targeted gene regions such as exons or other regions with known function (29). Combination strategies can also be utilized, such as combination of genome-wide scanning and candidate gene strategy, to improve the both efficiency and efficacy of studies, especially periodontal genetic studies, for which it is usually difficult to screen a large population. It should be kept in mind that our knowledge of FcγR genetics is expanding, new technology for detecting different kind of variation is continually

developed. The most important task for us before we dig in is to understand these new knowledge and technology thoroughly and find a way to incorporate these knowledge and technology with the unique nature of periodontitis. Only that can help us to establish a reasonable and practical strategy for association study in periodontitis.

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Table 1. General characteristics of human FcγRs

Receptor class	*kDa*	*Chromosome*	*Genes*	*Signaling motif*[a]	*Affinity for IgG (Ka)*
FcγRI (CD64)	72	1q21.1	FcγRIa	-	High (10^8-10^9/M)
			FcγRIb	-	
			FcγRIc	-	
FcγRII (CD32)	40	1q23-24	FcγRIIa	ITAM	Low (<10^7/M)
			FcγRIIb	ITIM	
			FcγRIIc	ITAM	
FcγRIII (CD16)	50-80	1q23-24	FcγRIIIa	-	Medium (±3×10^7/M)
			FcγRIIIb	-	Low (<10^7/M)

[a]ITAM: immunoreceptor tyrosine-based activation motif; ITIM: immunoreceptor tyrosine-based inhibitory motif.

Table 2. Factors that regulate human FcγRs and their actions

FcγRs regulatory function	*Factors*	*Reference*
Increase expression of FcγRI via upregulation of mRNA expression	GM-CSF IL-3 TNF-α	Okayama *et al*. 2000 (55) Pricop *et al*. 2001 (57) Radeke *et al*. 2002 (53)
Upregulate activating FcγRs and reduce FcγRIIb expression	C5a IFN-γ IL-1β TNF-α	Guyre *et al*. 1983 (52) Okayama *et al*. 2000 (55) Pricop *et al*. 2001 (57) Radeke *et al*. 2002 (53) Shushakova *et al*. 2002 (54)
Upregulate FcγRIIb expression on myeloid cells and downregulate FcγRIIb expression on activated B cells	IL-4	Rudge *et al*. 2002 (59)
Upregulate inhibitory FcγRIIb and reduced expression of activating FcγRs on innate effector cells	IL-5 IL-10 IL-13 TGF-β	Okayama *et al*. 2000 (55) Pricop *et al*. 2001 (57) Radeke *et al*. 2002 (53) Tridandapani *et al*. 2003 (58) Nimmerjahn *et al*. 2005 (56)

Table 3. Summary of findings from studies of association between human FcγR genes and periodontitis[a]

Periodontitis	*Population*	*FcγRIIa*	*FcγRIIb*	*FcγRIIIa*	*FcγRIIIb*	*References*
Aggressive (early onset)	Caucasian	+	ND	+	-	Loos *et al*. 2003 (31)
		-	ND	-	+	Nibali *et al.* 2006 (84)
	African-American	-	ND	-	+	Fu *et al*. 2002 (80)
	Japanese	-	ND	-	+	Kobayashi *et al*. 2000 (81)
		ND	+	ND	ND	Yasuda *et al*. 2003 (89)
	Chinese	+	ND	ND	-	Chung *et al*. 2003 (77)
	Brazilian	+	ND	ND	+	de Souza *et al.* 2006 (79)
Chronic (adult)	Caucasian	+	ND	-	-	Loos *et al*. 2003 (31)
		+	ND	ND	ND	Yamamoto *et al*. 2004 (88)
		-	ND	ND	-	Wolf *et al.* 2006 (87)
	Japanese	-	ND	-	-	Kobayashi *et al*. 1997 (82)
		ND	ND	+	ND	Sugita *et al*. 1999 (86)
		ND	+	ND	ND	Yasuda *et al*. 2003 (89)
		ND	+	ND	ND	Honma *et al.* 2008 (91)
	Chinese	-	ND	ND	-	Chung *et al*. 2003 (77)
Severe chronic (adult)	Caucasian	+	ND	+	-	Meisel *et al*. 2001 (83)
		+	ND	-	-	Loos *et al*. 2003 (31)
		+	ND	ND	ND	Yamamoto *et al*. 2004 (88)
	Japanese	-	ND	+	-	Kobayashi *et al*. 2000 (81)
	Chinese	-	-	+	-	Chai *et al.* 2010 (76)

Recurrent	Caucasian	-	ND	-	-	Colombo *et al*. 1998 (78)
chronic	Japanese	-	ND	+	+	Kobayashi *et al*. 2000 (81)
(adult)		ND	ND	ND	+	Sugita *et al*. 2001 (85)

+: positive association reported; -: negative association reported; ND: not determined.

[a]No data available regarding *FcγRIa*, *FcγRIb*, *FcγRIc*, *FcγRIIb*, *FcγRIIc* and *FcγRIV* polymorphism and periodontitis.

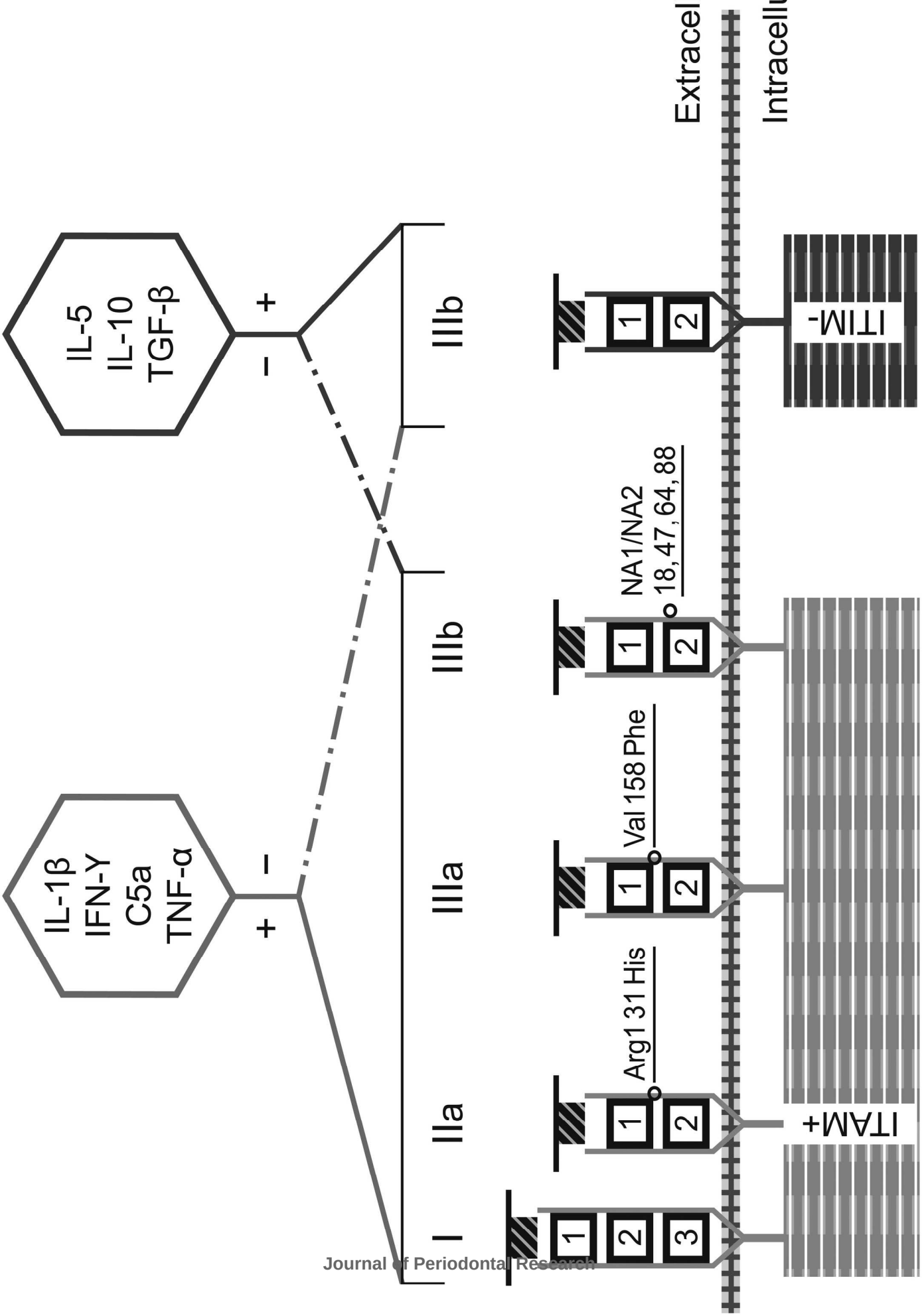
Legends

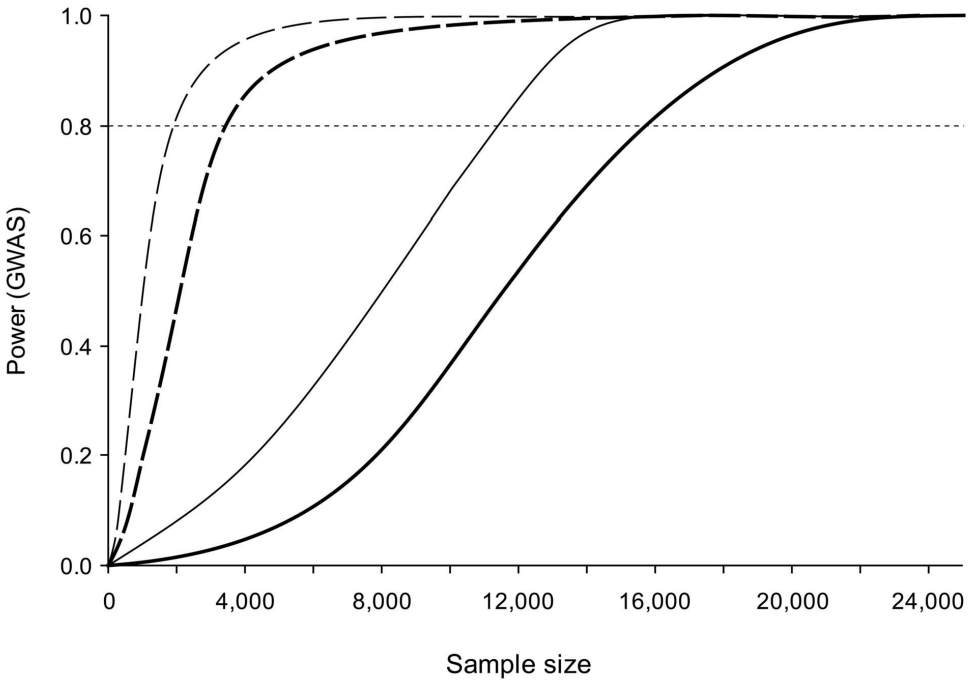
Fig. 1. Impact of mutation or variations on disease phenotype for Mendelian or complex diseases. **A**. In Mendelian diseases, mutation in a single dominant gene is necessary and sufficient to produce the clinical phenotype and cause disease. **B**. In complex disorders with multiple causes, variations or mutations in a number of genes encoding different proteins result in a genetic predisposition to a clinical phenotype. Pedigrees reveal no Mendelian inheritance pattern, and gene mutations are often neither sufficient nor necessary to explain the disease phenotype. Environment and behavioral factors are major contributors to the pathogenesis of complex diseases (151). Box(es): gene(s) involved; arrow: genetic mutation or variations.

Fig. 2. The power of a genome wide association study (GWAS) is determined by study sample size, minor allele frequency (MAF) as well as the odds ratio of the risk variant. This figure demonstrated when a disease with 0.5-1% prevalence (solid lines, e.g. aggressive periodontitis) and the risk variant odds ratio is 1.2, the relationship between the expected power and sample size under different MAFs. It showed when MAF is 0.2 (light solid line), sample size over 11,000 cases and 11,000 controls could reach an accepted power of 0.8. However when MAF is dropped to 0.1 (dark solid line), the required sample size is increased to 16,000 both case and control subjects (28). When a disease is with 15-20% prevalence (dash lines, e.g. chronic periodontitis) and risk variant odds ratio is 1.2, MAF of 0.1-0.2 (between light and dark dash lines) means sample size of 1,500 – 3,000 cases and controls could reach an acceptable power of 0.8. Therefore most of the GWAS today, particularly those for periodontitis, may not have sufficient power to detect genetic association of complex diseases with small effects.

Figure 3 Fc-gamma receptors and their regulatory factors. FcγI, FcγIIa, IIIa, and IIIb are immune activation receptors. FcγIIa activates an immune response through a immunoreceptor tyrosine-based activation motif (ITAM). FcγIIb is the inhibitory receptor and mediates an immune response via an immunoreceptor tyrosine-based inhibition motif (ITIM). The most studied polymorphisms are labeled on corresponding receptors. The left hexagon indicates factors that activate those activating receptors but inhibit FcγIIb. In the right hexagon are factors inhibit activating receptors but enhance inhibition of FcγIIb. The solid line means upregulation while dash-dotted line means downregulation. Influence of other minor regulatory factors like GM-CSF, IL-3, IL-4 and IL-13 were not included.

A. Mendelian disease
Genetic nature
Gene
Phenotype
100%
B. Complex disease
Genetic nature
Gene A
Gene B
Gene C
Gene D
Phenotype
A
B
C
D
Environmetal/
behavioral
factors


IL-5
IL-10
TGF-β
IL-1β
IFN-Y
C5a
TNF-α
+
−
−
+
IIIb
IIIb
IIIa
IIa
I
Extracellular
Intracellular
ITIM-
ITAM+
NA1/NA2
18, 47, 64, 88
Val 158 Phe
Arg1 31 His
1
2
3



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