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Genetic polymorphisms and periodontal disease in populations of African descent: A review

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Abstract

Aggressive periodontitis is a rare but rapidly progressing form of periodontal disease that usually affects otherwise systemically healthy individuals, at a young age. It usually affects first molars and incisors, which are usually lost if treatment is not properly and early rendered. Although of low prevalence, it affects individuals of African descent at a higher prevalence, and usually multiple members within the same family. Several studies have been performed in the attempt to evaluate specific single nucleotide polymorphisms (SNPs) that could be associated with this disease. To the best of our knowledge, the present article provides the first review of the literature focusing on studies that evaluated SNPs in patients of African descent with aggressive periodontitis. Several SNPs have been evaluated in different genes according to their role in the pathogenesis of the disease, with positive and negative associations (such as *IL1*, *FCGR3B*, *FPR1*, *LTF*, *CYBA*, *GLT6D1*, *TLR4*) with both the localized and generalized forms of aggressive periodontitis. Given the complexity of periodontitis, the difficulty in gathering large cohorts diagnosed with this rare form of disease, and the fact that candidate gene studies may only determine part of the genetic risk of a disease, the search for specific SNPs associated with aggressive periodontitis seems to be a long one, most likely to result in the combination of multiple SNPs, in multiple genes.

Keywords

African descent; African-Americans; aggressive periodontitis; periodontitis; single nucleotide polymorphisms

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CONFLICT OF INTEREST

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1 | INTRODUCTION

Periodontitis, commonly referred to as “gum disease,” is an infectious, inflammatory disease affecting the periodontium, the supporting tissues around teeth. Bacteria are believed to play a primary etiological role in this disease, although the host response seems to be responsible for most of the tissue destruction.[1] Periodontitis is considered a complex disease, which presents mostly a relatively mild phenotype, and is slowly progressive and chronic in nature, except for aggressive periodontitis (AgP, which can be generalized [GAP] or localized [LAP]). Periodontitis is the most common oral infection in humans and the major cause of tooth loss in adults.[1] Data from the 2009 and 2010 National Health and Nutrition Examination Survey cycles estimated that over 47% of the adult population in the United States has periodontitis.[2] Specifically looking at AgP, a 1987 National Institute of Dental Research examination of 11 007 US children aged 14–17 years reported that black children were 15.1 times more likely to have LAP than white children, and 24.6 times more likely to have GAP.[3] Another study found that the rate of AgP in African-Americans was 3%, compared to <1% for Caucasian-Americans.[4] This ethnic disparity appears to extend to other parts of the world as well: in a study of 1200 high school students in Sudan, the prevalence of AgP was significantly higher in students of African heritage compared to Afro-Arab descent (6% vs 2.3%, $P = .01$).[5] Thus, the literature consistently indicates that individuals of African descent are more prone to periodontitis, particularly AgP.

The etiology of periodontitis is related to the interaction between microorganisms and host responses. Specific periodontal pathogens, such as *Porphyromonas gingivalis*, *Tannerela forsythia*, *Aggregatibacter actinomycetemcomitans*, *Treponema denticola* and their lipopolysaccharides are well-known initiators of inflammatory and immune responses in the oral cavity.[6] However, their presence cannot explain differences in disease severity in the population. Löe et al[7] evaluated the natural history of periodontal disease over a 15- year period in a homogeneous population of Sri Lankans and found a range of progression rates, supporting the existence of different levels of host susceptibility to infection. In corroboration of this hypothesis, and consistent with the racial prevalence differences reported above, studies of twins suggested that genetic factors may account for a considerable part of individual variation in host response to periodontal infection.[8,9]

Complex diseases (also referred to as multifactorial) involve multiple biological pathways contributing to similar clinical phenomena. Variations in multiple genes are thought to each contribute a small degree of risk for complex diseases (polygenic). Therefore, such genes/variants are considered susceptibility or disease-modifying loci.[10] Similar to other complex diseases, it is estimated that, for periodontitis, at least 10 and possibly 20 or more genetic loci may be involved.[11] However, the number and types of relevant genetic variants may vary for different forms of periodontitis and different ethnic populations; their effects may also be influenced by environmental factors (gene- environment interactions).[11] A number of studies have been published investigating the association of genes and their variants (polymorphisms) in susceptibility to, or host responses in, periodontitis.

2 | GENETIC POLYMORPHISMS IN COMPLEX CONDITIONS

Polymorphisms may cause a change in a gene's encoded protein, or its expression, possibly resulting (directly or indirectly) in alterations in innate and adaptive immunity. Polymorphisms consisting of a base change are commonly called single nucleotide polymorphisms (SNPs), such that there are 2 versions (alleles) with the less frequent having a population frequency of at least 1%.[12] Polymorphisms may contribute to disease outcome and/or presentation, which can also be through conferring a degree of risk or protection from the disease. SNPs can also have no functional effect, being completely neutral. SNPs occur throughout the genome, with the most relevant for periodontitis thought to be those in genes that encode cytokines, receptors, metabolic regulators and proteins related to innate immunity.

SNPs can be tested for association with phenotypic changes in complex disease research.[11] The exact status of an SNP in a person is called the genotype. For example, if an SNP is known to have a C or T at its site in the genome (the 2 versions, called alleles), a given person could have a genotype of CC, CT or TT (1 allele from each parent, for non-sex chromosomes). Statistical methods analyze these genotype and allele frequencies with clinical features in patients, comparing also to control (unaffected) individuals, to test for associations. These methods typically involve amplification of the target DNA sequence followed by detection using fluorescence and/or gel electrophoresis.[12]

Genotyping technology has been evolving from low-throughput technologies that require more laboratory labor, to high-throughput technology, which can also include microarrays and can genotype millions of SNPs (genome-wide) in large sets of subjects, accurately and fairly cost-effectively. For smaller subject sets, however, low- and medium-throughput genotyping technologies screening candidate gene polymorphisms is the typical approach.

Candidate gene association studies utilize SNPs in genes whose function logically relates to the phenotype, testing for statistical relationships between the genotypes and the disease. If a genotype (or allele) has a statistically significant higher frequency in cases compared to controls, it suggests that this SNP is within a disease susceptibility locus or that there is linkage disequilibrium between this marker and the disease susceptibility locus. However, candidate gene studies may only determine part of the genetic risk.[13] A number of genes may actually contribute to a disease, but because of unknown contributory functions (lack of previous knowledge), some are not selected among the candidate genes, and can only be discovered through additional basic studies or genome-wide association studies (GWAS).[14]

As the allele frequencies at genetic polymorphisms often vary between ethnic populations, positive associations between an SNP and disease within 1 population may not necessarily predict association in other populations. Thus, ethnic/racial background is an important co-factor in such analyses, particularly in small studies. The International HapMap Consortium has been gathering allele frequency data from populations with ancestry from parts of Africa, Asia and Europe, to facilitate association studies.[14] Of particular interest is the putative role of genetic susceptibility in the increased rate of periodontitis in African-Americans. Thus, this review provides the first comprehensive summary of the literature

focusing on genetic association studies of susceptibility to AgP in African-Americans, and other populations of African descent. PubMed and PMC databases were searched with combinations of the search term “aggressive periodontitis,” with one or more of the terms “African,” “African-American,” “Black,” “susceptibility,” “genetic association” and “GWAS,” to identify original publications of genetic association studies in AgP focusing on individuals with African ancestry.

3 | CANDIDATE GENE STUDIES IN AGGRESSIVE PERIODONTITIS

Many of the candidate studies in AgP have focused on genes encoding proteins that play a role in recognition and clearance of bacteria by the immune system, tissue destructive processes or metabolic mechanisms. For example, studies have implicated polymorphisms in the Fc gamma receptor genes and interleukin genes.[15–17] Once genes are decided, SNPs within them are chosen based on known or predicted functional effect, previous reports and reasonable allele frequency in the population to be studied. Table 1 provides a summary of the published association studies of candidate gene polymorphisms in AgP that included subjects who were African-American or African descent; in some cases, these studies also examined other races and/or chronic periodontitis, and these data are in Table 1 for comparison. For maximum specificity, the table lists the SNPs by their unique identifying “rs” numbers, with the text of this article describing the informal, imprecise names used by some of these articles.

3.1 | Interleukin genes

Interleukin-1 (*IL1*) is a proinflammatory mediator mainly released by monocytes, macrophages and dendritic cells. The genes encoding the proteins IL1α, IL1β and interleukin receptor antagonist are located in close proximity at the *IL1* gene cluster on chromosome 2. The following *IL1* polymorphisms have been studied in association with periodontitis in Africans/African descent: *IL1A* promoter −889 (rs1800587 C/T), *IL1A* +4845 (A/G rs1143633; note that this is actually in an intron of *IL1B* and called *IL1B* +3877 in some reports), *IL1B* promoter −511 (rs16944 A/G), *IL1B* promoter −1464 (rs1143623 C/G), *IL1B* promoter −3737 (rs4848306 A/G), *IL1B* +3954 (also referred to as +3953, rs1143634 C/T), *IL1RN* intron (A/G, rs419598 C/T) and *IL1RN* intron 2 repeat-length polymorphism (rs2234663).

The oldest study[18] examined SNPs rs1800587 (*IL1A*) and rs1143634 (*IL1B*) in a genetic analysis of 28 African-American families with AgP in at least 2 individuals, finding that the C allele of each SNP was transmitted to offspring with periodontitis much more often than the other allele ($P = .0065$ for rs1800587, $P = .0005$ for rs1143634).[18] This was followed by a study of one of the same SNPs (rs1143634) and rs1142633, which are both in *IL1B*, in a case-control study of 37 affected (LAP) and 104 healthy African-Americans; however, no association was found in this analysis.[19] In 2003, Guzman et al[20] screened 100 American diabetic patients for periodontitis, to test for association with the 4 SNPs shown in Table 1 (*IL1A, IL1B, ILRN*). Within this group were 66 affected individuals (some severe disease, others moderate, 23 being African-American) and 34 healthy (6 African-Americans). The only genetic association identified suggested that the G allele of −511 *IL1B* rs16944 confers

risk for periodontitis in African-Americans. In 2011, a Brazilian analysis studied rs1800587 (*IL1A*), rs16944 (*IL1B*), rs1143634 (*IL1B*) and rs2234663 (*ILRN*).[21] However, there were only 3 healthy and 10 affected African-Americans in the study. This group found that rs16944 allele T was associated with chronic periodontitis in the African-Americans combined with Mulatto subjects (mixed black and Caucasian ancestry) ($P = .018$), which is in contrast to that found by Guzman et al. The genotype "2/2" of the *ILRN* microsatellite marker rs2234663 was associated with the severity of disease in the group as a whole but not risk of disease. Wu et al[22] analyzed *IL1B* SNPs (see Table 1) in 4 ethnic groups (151 affected with chronic periodontitis and 71 healthy African-Americans), including haplotype and diplotype analyses and meta analysis of several other studies, reporting that diplotype "3" from rs16944, rs1143623 and rs4848306, in combination with specific genotype at rs1143633, is associated with disease. Greater significance was found when adjusting for co-factors of smoking and diabetes. Boukortt et al[23] recruited 151 Algerians (nearly all non-smokers) with chronic (n = 91) or AgP (n = 60), and 128 healthy subjects into their study of *IL1A* rs1500587 and *IL1B* rs1143634. When stratifying the cases by type of periodontitis, the frequency of the T allele of each SNP was significantly higher in the AgP group compared to control and chronic periodontitis ($P = .03$ and .01 respectively). Although Algeria is in northern Africa, genetically this population is more similar to Arabic countries with some European admixture, so is somewhat different from African-Americans whose ancestors came mostly from West Africa.[24]

IL4 encodes the proinflammatory cytokine IL-4; 2 SNPs were found in association with asthma and atopy, and later with AgP in Caucasians.[25,26] Scarel-Caminaga et al[27] analyzed rs2243250 (C/T promoter −590) in 44 healthy and 69 affected (chronic periodontitis) Brazilian subjects and found no associations, including within the African-American subgroup. Another study of 30 healthy and 30 affected Brazilians, in 2004, examined the same *IL4* SNP and another variant in an intron (70 bp repeat-length polymorphism, rs8179190), and found no associations.[28]

A group in the UK studied polymorphisms in the IL-6 gene (*IL6*), encoding another proinflammatory cytokine, which resulted in 2 publications. In the 2008 study of families (12 black, 43 other ethnic background), consisting of screening for affected status in first-degree relatives of probands with AgP, 53% of those relatives were found to have periodontitis in general, with 10% of relatives specifically having AgP.[29] The overall genetic association analysis (transmission disequilibrium test) was not significant for the 3 SNPs analyzed: rs1800795 (G/C promoter −174), rs2069827 (G/T promoter −1363), and rs2069825 (2 bp insertion/deletion variant, promoter −1480). However, there was a trend for association with homozygosity for the minor alleles (genotypes GG, GG, homozygous deletion respectively). In the 2009 study from the same group, 5 *IL6* SNPs were examined in larger subject sets: the same 3 evaluated in the previous study along with 2 others (rs1800796, G/C promoter −572 and rs4719714, A/T promoter −6106).[30] Among their cohort of 93 affected and 45 healthy blacks, no associations were found with individual SNPs and diagnosis of periodontitis. However, in the Caucasian subjects in their study, the combined genotypes of rs1800795 (GG) and rs2069827 (GG) showed a weak association with periodontitis ($P = .044$), and there were some limited haplotype associations as well. Regarding the diagnosis of LAP, statistically significant associations were detected between

LAP and healthy controls in Caucasians (144 healthy controls and 24 patients with LAP) for 1480 ($P = .007$), and 6106 ($P = .010$), polymorphisms controlling for gender and smoking differences, and for the haplotype made up of all 5 SNPs ($P = .01$) and for a model including only 1363 and 1480 ($P = .001$). However, these associations were not found in black people.

The IL-8 gene (*IL8*), encoding proinflammatory chemokine IL-8, was examined in three Brazilian studies. Andia et al genotyped the rs4073 polymorphism (A/T, promoter −251, also called −353 depending on numbering system) with the first study (2011) testing 181 affected with chronic periodontitis (12 African-Americans) vs 108 healthy (14 African-Americans). This study found evidence of association of the AT genotype with increased risk of periodontitis, with "A" being the risk allele.[31] However, the second study, a combination of family-based and case-control analyses with GAP, had no significant findings, even among the African-American subset.[32] Sippert et al[33] analyzed the same SNP as well as 2 others, rs114259658 (A/T promoter −738) and rs2227532 (C/T promoter −845) in a set of 197 healthy controls (14 Afro-Brazilians, 45 Mulatto) and 124 affected (chronic periodontitis, 15 Afro-Brazilians, 37 Mulatto). There were no associations with disease in either group, although in the entire study (not broken down by ethnic group), the rs2227532 C allele was associated with disease, as was the *IL8* haplotype CTA (alleles from rs2227532, rs114259658, rs4073, respectively), but only among non-smokers.

3.2 | Formyl peptide receptor gene

The *FPR1* gene was also examined in several studies; this gene encodes the high-affinity N-formyl peptide receptor, which is involved in attracting monocytes to sites of infection and mediating degranulation. These processes are thought to be abnormal in AgP, and thus genes controlling the function of this process are logical candidates.[34] The first reported study was by Gwinn et al;[35] however, the SNPs described by this group could not be identified/replicated by Zhang et al[36] and we found that most of the reported primer sequences did not map to the *FPR1* gene. Zhang et al's group[36] examined 6 SNPs in the coding region of this gene: rs2070745 (c.301 G>C encoding Val101Leu), rs28930680 (c.306 T>C a synonymous substitution at Phe102 discovered and reported in that publication), rs5030879 (c.348 C>T encoding synonymous Ile116), rs2070746 (c.546 C>A synonymous substitution at Pro182), rs5030880 (c.568 A>T encoding Arg190Trp) and rs1042229 (c.576 T>CorG encoding Asn192Lys). All of these polymorphisms are in exon 2, in linkage disequilibrium. The study included 111 individuals with AgP (38 African-Americans) and 115 healthy subjects (23 African-Americans), with the other 2 ethnic groups being Turkish and Brazilian. Some of the subjects' disease was LAP and some had GAP, but statistics based on that phenotype were not presented. The C allele of rs28930680 was associated with AgP in the Turkish population ($P = .0139$), and the T allele of rs5030879 was associated in the Brazilians ($P = .0158$). In African-Americans, the AA genotype of rs5030880 was associated with AgP ($P = .0033$), as was the genotype consisting of 1 or 2 copies of the Lys allele of rs1042229 (C or G, $P = .0018$). These latter 2 SNPs were investigated further through haplotype analysis, and not surprisingly the AG (Arg/Lys) haplotype was associated with AgP in African-Americans ($P = .0002$) but not in the other populations. The TC haplotype (encoding Trp/Asn) was actually under-represented in the African-Americans and thus could be protective. A group in Europe reported analysis of 3 *FPR1* SNPs (rs2070745, rs2070746, rs5030880), in 224

subjects with LAP or GAP (59 black) and 231 healthy controls (45 black).[37] None of these SNPs or haplotypes was significant in any of the groups. The other 2 FPR1 reports came from the same group, with 1 study detecting association of the T allele of rs5030879 with AgP in 37 affected and 38 healthy African-Americans ($P = .017$).[34] A few additional SNPs were tested for the haplotype effect but the P value failed to change, suggesting that the rs5030879 SNP was contributing the most effect. This group's other publication reported analysis of the same 6 SNPs as Zhang et al's group, in another set of 30 AgP and 33 healthy African-Americans as well as a set of Turkish subjects.[38] The T allele of rs5030879, and the TT genotype, were associated in African- Americans ($P = .021$), as well as some 2-point haplotypes involving that SNP. This group examined *FPR1* mRNA levels in polymorphonuclear leukocytes from patients with different genotypes, but found no difference, suggesting that the risk mechanism is not through gene expression. Thus, the Ile116 synonymous variant has been implicated by several studies in AgP in people of African descent. If this effect is real, it is unclear whether this variant somehow affects protein function or is tightly linked to another variant that confers the effect.

3.3 | Fc gamma receptor genes

The genes encoding the FC gamma receptors (subclasses 2A, 2B, 3A, 3B) have also been of interest because these receptors bind the constant portion of immunoglobulin G and are involved in the host response to bacterial infection. Three studies were found that examined SNPs in these genes. In 2002, Fu et al studied rs1801274 of *FCGR2A* (Arg (G)131 > His (A)), rs396991 in *FCGR3A* (Phe (G)138 > Val (T)), and 5 linked SNPs in the same exon of *FCGR3B*: rs403016 (Ser (C) 36 > Arg (G)), rs447536 (C>T synonymous Leu74), rs448740 (Asn 65(A) > Ser (G)), rs428888 (Asp (G) 118 > Asn (A)) and rs2290834 (Ile (A) 106 > Val (G)).[39] The African-American participants in this study were diagnosed with LAP[40] and 67 were healthy individuals. The "NA2" haplotype of *FCGR3B* (alleles CTGAA in *cis* such that protein encoded from the haplotype contained SerLeuSerAsnIle at those residues) and the NA2/NA2 genotype was associated with the risk of disease ($P = .024$). A European group also examined the same *FCGR* SNPs as the previous study, plus rs1050501 of *FCGR2B*, in their set of 59 AgP affected and 45 healthy black people (plus Caucasians and Asians).[37] An association of the NA1/NA1 *FCGR3B* diplotype was associated with GAP in Caucasians, and in that group, an interaction of the NA1 haplotype and the T allele of another gene SNP (*CYBA* gene encoding NAPDH p22phox, rs4673 Tyr(T) 72>His (C)) was found with an odds ratio (of being affected) of 30.3 for individuals homozygous for these alleles. There were no significant results regarding LAP, and no significant results for the subset of African-Americans. As an aside, this group also tested for an association with the *FCAR* gene (Fc alpha receptor, rs1865096 encoding silent Arg108 variant), and found no significant results. Finally, Song and Lee (2013)[41] performed a meta-analysis of the *FCGR2A*, *FCGR2B* and *FCGR3B* results in periodontitis from 17 studies, with over 1400 combined Caucasian, Asian and African patients and controls (210 African affected, 224 healthy). They found that they *FCGR2A* rs1801274 combined genotypes AG (His/Arg at 131) and GG (Arg/Arg at 131) were associated with disease compared to the AA genotype, but only in Caucasians ($P < .0001$), with a dominant model, but not when broken out by AgP vs chronic periodontitis. However, these authors also detected evidence of publication bias suggesting that underlying issues with the Hardy-Weinberg equilibrium in a few studies (but

none with African cohorts) could artificially inflate the significance of this SNP. There was moderate evidence for association of periodontitis with the *FCGR3A* Val (T) allele in Caucasians ($P = .042$), which held up in the genotype test (Val/Val + Val/Phe vs Phe/Phe) in Caucasians in a dominant model ($P = .02$). For *FCGR3B*, the meta-analysis showed 2 associations: first, there was a strong association of the NA2 allele ($P = 2 \times 10^{-9}$) and NA2/NA2 genotype ($P < 10^{-6}$) in South Asians only, regardless of model. Second, when the cases were stratified by type of periodontitis, the NA2/NA2 genotype was associated with AgP in a recessive model regardless of ethnicity ($P = 1.1 \times 10^{-5}$). Thus, the NA2 haplotype is implicated as a risk allele in at least several candidate gene studies, meriting further study with larger cohorts and biochemical analysis of the functional differences of the proteins encoded by the different haplotype.

3.4 | Other genes

Two groups studied polymorphisms in lactoferrin (encoded by the *LTF* gene), a protein that plays a role in the innate immune system. One examined rs1126478 (Arg (G) 47 > Lys (A)) in a study of 9 LAP affected (7 African-Americans) and 17 healthy (6 African-Americans), and found an association with the group as a whole and just among African-Americans ($P < .02$).[42] The other study analyzed rs1126477 (Ala(G) 29 > Thr(A)) in a group of affected individuals (77 Caucasians, 46 African-Americans) and healthy individuals (131 Caucasians, 78 African-Americans), and found association of the G allele with AgP, but only in the African-Americans.[43]

Two groups pursued analysis of vitamin D receptor SNPs. Nibali et al[44] examined rs731236 (silent Ile 352, C>T) in 244 subjects with AgP (59 black), 79 with chronic periodontitis (6 black), and 231 healthy controls (45 black). There were no significant case-control associations with the SNP, although an interaction between the T allele and smoking was associated with the disease ($P = .033$). Hashim et al[45] failed to find association with the rs2228570 SNP (Met (T) 1 > Thr (C)) in Sudanese subjects with AgP.

The Brazilian group that examined the 3 *IL8* SNPs listed above also tested polymorphisms in the Duffy blood group locus atypical chemokine receptor (*ACKR1*, also known as DARC), as is involved in the IL- 8-mediated immune response.[33] The SNPs included rs12075 (c.125 G (Gly 44) > A (Asp)), rs34599082 (c.265 C(Arg 91) > T (Cys)), rs13962 (c. 298 G (Ala 102) > A (Thr)), rs2814778 (5′ UTR -67 upstream translation start, T/C). However, no associations with *ACKR1* were found in the Afro-Brazilian or Mulatto subgroups, by SNP or haplotype.

The other 2 genes reported in African-American/African descent association studies were *GLT6D1* (glycosyltransferase 6 domain containing 1, expressed in leukocytes and gingiva and thought to be involved in GATA3 signaling in immune cell development) and *TLR4* (toll-like receptor 4, recognizes lipopolysaccharides produced by certain bacteria to stimulate an immune response). Hashim et al,[45] who studied the Sudanese AgP affected/control group described above (132 AgP and 136 controls), chose rare SNPs in these 2 genes for analysis: The *GLT6D1* SNP rs1537415 was chosen because the G allele was found to be strongly associated in a GWAS analysis of Caucasians with periodontitis.[46] This group

found a significant association of AgP cases with the G allele ($P = .0295$).[40] Another study looked into rs1126477[43] and found the G allele associated with AgP ($P = .0007$).

Another study found a glycosyl transferase gene (GLT6D1) associated with AgP in an African population. The authors then added 147 more healthy controls from a Yoruban (African) population, and the re-analysis showed significance that withstood multiple testing corrections ($P = .013$). This is one of the few examples of associations that appear to hold true in multiple ethnic groups. *TLR4* SNP (rs4986790, Asp259 (A) > Gly (G)) was chosen due to its previous associations with strong inflammatory responses in vitro, and the G allele was found associated with AgP disease in this study set as well ($P = .0053$).[45]

4 | DISCUSSION AND FUTURE PERSPECTIVES

A 2012 comprehensive review of periodontitis genetic association studies that was written in English with case-control design found 164 publications in PubMed presenting data from over 250 different polymorphisms.[11] However, only 9 studies at that time were identified as studying "African-Americans," and only one was considered adequately powered. In examining other reviews, there was little additional information about AgP in patients of African descent. The meta-analysis in Song et al[47] analyzed the combined effect of 2 of the Nibali *TNF* studies and found no significance. The *IL8* meta-analysis by Chen et al included 3 of the studies described here[31–33] but the only significant observation was that T allele rs4073 was associated with increased risk of periodontitis in a Brazilian mixed population (includes some African background), which also showed marginal association of the other *IL8* SNP (rs2227532).[48] The studies reported in this review nearly all had small subject numbers: most had fewer than 70 affected individuals (some much less), particularly of African descent. That factor, combined with the relative rarity of some of the alleles in those of African descent, suggests that negative studies do not necessarily rule out an effect, and likewise, positive results should be interpreted with caution. This is also reflected in the relatively weak *P* values for most of the associations. However, a meta-analysis can compensate for this lack of power provided the diagnostic criteria are consistent. In fact, the Song and Lee meta-analysis (of case-control association studies in all races) had results with much more impressive *P* values.[41] There were no sex-based differences reported in any of the studies, although some did not stratify for gender due to the low sample size. Most of the studies that examined more than 1 gene (unlinked loci) appropriately used correction for multiple tests (which dramatically reduces power) and reported consistency with Hardy-Weinberg equilibrium. Additionally, those that had multiple linked loci also tested for associations with haplotypes/diplotypes. These associations can detect synergistic *cis*-acting effects but also results in less power due to additional alleles (haplotypes). Unfortunately, the linkage disequilibrium between markers that were haplotyped was not always provided in these studies. This can be useful information for future studies in this area. Another point of consideration is that the SNPs examined do not completely cover the genes of interest. In fact, some were limited to the promoter region. Thus, other parts of the gene that were not in strong linkage disequilibrium with the chosen SNPs, and were not examined, could still harbor a functional effect on disease risk. Furthermore, another factor to consider was that some of the alleles were relatively rare in the subjects of African descent, which is more likely to lead to spurious results or miss a potential association. For example, from the

studies listed in Table 1, for subjects of African descent, the frequency of the T allele of *ILB1* rs1143634 was 0.08–0.12, the frequency of the minor allele at *FPR1* rs5030880 was less than 0.05, and the frequency of the C allele at *IL8* rs2227532 was only 0.03. Thus, any error introduced by genotyping methods, for instance, could markedly affect results, particularly when SNP's alleles are complements (eg, C and G).

As illustrated by some of the results of these studies, differences among races must also be considered when evaluating association data, and in project design. In the studies reported here, racial grouping is based on self-reported ethnic background. However, this can be misleading in people who actually have a mixed background, which includes nearly all African-Americans. One method to address this is the use of specific ancestry-informative markers to identify the relative percentage of ancestry based on DNA, such as described in Kosoy et al.[40] Although this is not commonly performed in small studies, such as most reported here, it is an important consideration as self-reported race can vary from ancestry-informative marker data, and can encompass a very wide range of percentages of different ancestry.[49] This is particularly critical for alleles with a large difference in frequency based on race, such as the *IL6* rs1800795 SNP in which (per dbSNP) the C allele is absent in sub-Saharan Africans, less than 3% in African- Americans, but has a frequency of 55% in American Caucasians. Such differences could skew association results, and may explain why many small candidate gene positive results are not reproducible. Furthermore, it is important to include other factors in the analysis, such as the type of periodontitis and risk factors (eg, smoking and diabetes were revealed to be important co-factors in several studies). High-quality, strict criteria phenotype information is critical, because even a few misdiagnoses could lead to a false positive or false negative result. The finding of an association in an ethnic group in 1 study but not another, or positive signal in 1 ethnic group but not a different group, does not necessarily invalidate the positive findings. In fact, even the detection of different risk alleles from an SNP in different populations can be consistent with true association, if there are interacting factors involved that differ among populations, or a different degree of pathways involved in the phenotype;[50] an example of that is possible different associations of chronic vs LAP vs GAP.

Thus, factors such as the ones indicated above contribute to interpreting the results of the studies in this review. For example, The *IL1A/B/RN* locus was studied by several groups. However, there were some conflicting results, such as the African-American family study implicating the rs1800857 C allele in periodontitis,[18] while the Boukortt et al study[23] found an association of the T allele with disease risk in Algerians. Another example was regarding rs16944 in *IL1B*, where heterogeneity was also found: Guzman et al[20] identified the G risk allele in African-Americans only, while another group found evidence for the T allele,[21] and Wu et al[22] only found significance for this SNP in diplotype combinations (some of the SNPs were in linkage disequilibrium). Wu et al's study included larger numbers, in a meta-analysis, as well as individual SNP and haplotype/diplotype analyses, which led to stronger *P* values in multiple ethnic groups. A similar conflict was seen in results at the *LTF* locus, with opposite alleles implicated.[41,43] The Song and Lee meta-analysis[41] had the most power and was the only 1 to identify an association with individual SNPs or haplotypes in the *FCGR* locus (although mostly in Caucasians). There are numerous possible reasons for these

observations, and when multiple studies have agreement, it is reassuring that the association results are potentially real and are worth pursuing further.

As the main weakness of the candidate gene studies was low subject enrollment, the meta-analyses were particularly useful because of the substantial increase in power. A meta-analysis can therefore compensate for multiple small candidate gene studies that do not reproduce each other's results. SNPs that showed significance in meta-analyses in the groups with AgP and at least some of African ancestry are therefore most likely to reflect true susceptibility loci, such as *IL8* rs4073, *FCGR3B* haplotype and *IL1B* haplotype. However, the best confirmation of these findings would be positive results from a genome-wide association (GWAS) analysis with replication cohort, or a very large candidate gene study.

The best complement to the current candidate gene studies would be a GWAS analysis of sufficient numbers of individuals with AgP and healthy subjects of African descent, as it would provide an unbiased identification of genomic regions contributing to disease risk.[51] Such studies have not yet been done, possibly due to the difficulty in gathering a large cohort of the low prevalent AgP. Ideally, these data would also be used to stratify based on degree of common ancestry, to control for admixture. It would also be optimal to focus on a specific phenotype such as LAP, controlling for potential confounding factors (eg, diabetics and smokers). In chronic periodontitis, this type of approach has begun, as chronic periodontitis consists of a more common disease. For instance, Sanders et al[52] recently published a multi-ethnic GWAS study that found a statistically significant SNP in a set of Latino patients (in a non-coding RNA). Association with this SNP was tested and replicated in an African-American cohort (908 subjects), but not in a European-American cohort, illustrating that there may be different genetic susceptibility across races, or even that this may not be a true susceptibility locus. Further, variants implicated in 1 type of periodontitis might not be contributory in other types, depending on the biochemical pathways involved in these diseases. All of these factors must be taken into consideration in genetic studies. Once solid associations are found, within or among groups, researchers must work towards understanding the mechanistic basis for the disease susceptibility, which is likely to yield information that will eventually be translated to the clinic.

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TABLE 1

Genetic association studies of candidate genes in periodontitis in people of African descent

Reference	SNPs	Results
Diehl et al (1999)[18]	***IL1A*** rs1800587 ***IL1B*** rs1143634	Subjects: 28 African-American families. C allele of each SNP was associated with risk of *generalized aggressive periodontitis* (rs1800587 $P = .0065$, rs1143634 $P = .0005$). Trend for localized disease but not statistically significant
Walker et al (2000)[19]	*IL1A* rs1143633[a] *IL1B* rs1143634	Subjects: 37 affected (localized aggressive) and 104 healthy, African-Americans. *No association found*
Fu et al (2002)[39]	*FCGR2A* rs1801274 *FCGR3A* rs396991 ***FCGR3B*** rs403016, rs447536, rs448740, rs428888, rs2290834	Subjects: 48 affected (*localized aggressive*) and 67 healthy, African-Americans. *FCGR3B* "NA2" haplotype associated ($P = .024$) with disease (alleles C, T, G, A, A, respectively in same order as listed in SNPs column)
Zhang et al (2003)[36]	***FPR1*** rs2070745, **rs28930680**, rs5030879 rs2070746, rs5030880, **rs1042229**	Subjects: 38 affected (*aggressive periodontitis*), 23 healthy, African-Americans. Small Brazilian and Turkish set as well. Association with rs5030880 GG genotype ($P = .0033$) and rs1042229 CG + GG genotype in African-Americans with *localized disease*, but not others. rs5030879 T allele was associated in Brazilians but not others. Haplotype analysis of rs5030880 + rs1042229 was significant in African-Americans but no others ($P = .0002$)
Guzman et al (2003)[20]	*IL1A* rs1143633[a] *IL1B* rs1143634 ***IL1B* rs16944** *IL1RN* rs419598	Subjects: 100 diabetics: 66 affected (23 African-Americans), 34 healthy (6 African-Americans). rs16944 G allele associated with disease only in African-Americans. Type (generalized, aggressive) not indicated, just severity
Velliyagounder et al (2003)[42]	***LTF* rs1126478**	Subjects: Among 9 affected and 17 healthy total (7 affected and 6 healthy were African-Americans). A allele associated with *localized aggressive disease* in whole group and African-Americans alone ($P < .02$)
Scarel-Caminaga et al (2003)[27]	*IL4* rs2243250	Subjects: 44 healthy and 69 affected (*chronic periodontitis*) Brazilians including African-Americans (3 healthy, 10 affected), mulattos (3 affected, 2 healthy). No associations were found
Pontes et al (2004)[28]	*IL4* rs8179190 *IL4* rs2243250	Subjects: 30 affected (mostly *localized aggressive disease*) and 30 healthy Brazilians of African descent. *No associations*
Jordan et al (2005)[43]	***LTF* rs1126477**	Subjects: 46 affected and 78 healthy, African-Americans. G allele associated with *aggressive periodontitis* ($P = .0007$) (not in Caucasian case-control, 77/131)
Nibali et al (2006)[37]	*FCAR* rs1865096 ***CYBA* rs4673** *FPR1* rs2070745, rs2070746, rs5030880 *FCGR2A* rs1801274 *FCGR2B* rs1050501 *FCGR3A* rs396991 *FCGR3B* rs403016, rs447536, rs448740, rs428888, rs2290834	Subjects: 59 affected, 45 healthy, European blacks in a larger set including Caucasian, Asian, other. The *CYBA* SNP (NADPH oxidase p11phox) T allele associated with disease in total group ($P = .002$) and in Caucasians ($P = .009$), but was borderline in blacks ($P = .05$). For Caucasians with *generalized aggressive periodontitis*, the *FCGR3B* NA1/NA1 diplotype was associated under a gene-gene interaction (with *CYBA* T allele) such that subjects homozygous for both risk genotypes had odds ratio of 30.35 of having the condition. No SNPs significant in *localized aggressive periodontitis*
Nibali et al (2008)[29]	*IL6* rs1800795 *IL6* rs2069827 *IL6* rs2069825	55 families (12 blacks, 33 caucasians, 10 others) consisting of affected proband, and 100 first degree relatives who were evaluated for *aggressive periodontitis* (53% found to have periodontitis of some sort, 10% of relatives had aggressive periodontitis). A trend toward association with rs1800795 GG genotype and rs2069825 CC genotypes was found but was not statistically significant
Nibali et al (2008)[44]	*VDR* rs731236	Subjects: 224 *aggressive periodontitis*, 79 *chronic*, 231 healthy (Blacks: 59, 6, 45, respectively). No significant case-control differences, but interaction between SNP (T risk allele) and smoking was associated with periodontitis among all subjects ($P = .033$)
Nibali et al (2009)[30]	*IL6* rs1800795 *IL6* rs1800796 *IL6* rs2069827 *IL6* rs2069825 *IL6* rs4719714	Subjects: 93 affected and 45 healthy European Blacks (also a set of Caucasians and Asians). No associations with overall periodontitis and individual SNPs. Genotype GG of rs1800795 + rs2069827 together associates with disease in Caucasians only ($P = .044$). Limited associations of subgroups with haplotypes in Caucasians, particularly *localized periodontitis*
Maney et al (2009)[34]	***FPR1* rs5030879**	Subjects: 37 affected (*aggressive periodontitis*), 38 healthy African-Americans. T allele associated with disease ($P = 0.017$). Tested other nearby SNPs for

Reference	SNPs	Results
		haplotype effect on association (combined with rs5030879) but *P* values did not change from effect of that SNP alone
Maney and Walters (2009)[38]	***FPR1*** rs2070745, rs28930680**, rs5030879** rs2070746, rs5030880, rs1042229	Subjects: 30 affected (*localized and generalized aggressive disease*), and 33 healthy African-Americans, and set of Turkish subjects (healthy and affected). T allele and TT genotype of rs5030879 associated with disease risk in African-Americans ($P = .021$). Found some associations with 2-SNP haplotypes involving rs5030879
Trevilatto et al (2011)[21]	*IL1A* rs1800587 *IL1B* rs16944 *IL1B* rs1143634 *IL1RN* rs2234663 (microsatellite marker)	Subjects: Brazilians including African-Americans (3 healthy, 10 affected), Mulattos, Caucasians. Tested single SNP genotypes, combined haplotypes. Allele T of rs16944 associated with *chronic* disease in African-Americans + Mulattos combined ($P = .018$). Genotype 2/2 of rs2234663 associated with severe disease in all (but not overall disease risk)
Andia et al (2011)[31]	*IL8* rs4073	Subjects: Brazilians, 181 affected (*chronic periodontitis*), 108 healthy, in 4 ethnic groups including 14 healthy and 12 affected African-American. AT genotype conferred increased risk (not detailed by ethnic group), A is risk allele
Andia et al (2013)[32]	*IL8* rs4073	Subjects: 13 families with *generalized aggressive periodontitis*, and case-control (78 affected, 108 healthy), 3 ethnic groups (<20 in each of healthy and affected African-American case-control groups). *No significant findings*
Sippert et al (2013)[33]	*IL8* rs4073 *IL8* rs114259658 *IL8* rs2227532 *ACKR1* rs12075 *ACKR1* rs34599082 *ACKR1* rs13962 *ACKR1* rs2814778	Subjects: 197 healthy control (14 Afro-Brazilian, 45 Mulatto), 124 affected (*chronic periodontitis*, 15 Afro-Brazilian, 37 Mulatto). No individual SNPs or haplotypes significantly associated with disease in these populations. Overall, the *IL8* rs2227532 C allele and 3-SNP haplotype CTA were associated with disease but only in non-smokers
Song and Lee (2013)[41]	*FCGR2A* rs1801274 *FCGR3A* rs396991 *FCGR3B* rs403016, rs447536, rs448740, rs428888, rs2290834	Meta-analysis of 17 studies (3 having subjects of African descent). rs1801274 AG+GG genotype associated in Caucasians ($P = .000047$) in a dominant model. rs396991 G allele associated *only in Caucasians* (0.042). *FCGR3B* NA2 allele and NA2/NA2 genotype conferred risk for disease in *South Asians only*. The NA2/NA2 genotype was associated with aggressive periodontitis in the overall study under the recessive model ($P = 1.1 \times 10^{-5}$)
Hashim et al (2015)[45]	***GLT6D1* rs1537415** *IL1RN* rs4251961 *VDR* rs10735810 ***TLR4* rs4986790**	Subjects: 132 affected (*aggressive periodontitis*) and 136 healthy Sudanese. Significant association with *GLT6D1* G allele, even more so when included Yoruban healthy controls (147). *TLR4* SNP was significant ($P = .0053$) but is rare
Wu et al (2015)[22]	*IL1B* rs16944 *IL1B* rs1143623 *IL1B*rs4848306 *IL1B* rs1143633	Subjects: 151 affected (moderate to severe *chronic periodontitis*) and 71 healthy African-Americans, plus cohorts of Caucasian, Asian and Hispanic subjects. rs16944 and rs4848306 were individually associated, and the following haplotypes CGT, TGC of the first three SNPs were associated with disease. Diplotype "3" (haplotype combinations plus genotype at rs1143633: a composite genotype) was found associated with disease in Caucasians and African-Americans ($P < .0001$). A meta-analysis including other studies found association in Asians and Hispanics as well
Boukortt et al (2015)[23]	***IL1A* rs1500587** ***IL1B* rs1143634**	Subjects: Algerians (151 individuals with periodontitis [60 with aggressive form], 128 healthy controls). T allele of each SNP was associated with aggressive periodontitis compared to healthy ($P = .03$, $P = .01$ respectively). *Chronic periodontitis was not associated*

[a]This SNP actually lies in an intron of *IL1B*. Bold indicates significant association of gene/rs with aggressive disease in African-Americans. Periodontal condition and evaluated gene in italics.