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Identification of disease-associate variants of aggressive periodontitis using genome-wide association studies

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ABSTRACT

Aggressive periodontitis (AgP), Stage III or IV and Grade C according to the new periodontitis classification, is characterized by the rapid destruction of periodontal tissues in the systemically healthy population and often causes premature tooth loss. The presence of familial aggregation suggests the involvement of genetic factors in the pathogenesis. However, the genes associated with the onset and progression of the disease and details of its pathogenesis have not yet been fully identified. In recent years, the genome-wide approach (GWAS), a comprehensive genome analysis method using bioinformatics, has been used to search for disease-related genes, and the results have been applied in genomic medicine for various diseases, such as cancer. In this review, we discuss GWAS in the context of AgP. First, we introduce the relationship between single-nucleotide polymorphisms (SNPs) and susceptibility to diseases and how GWAS is useful for searching disease-related SNPs. Furthermore, we summarize the recent findings of disease-related genes using GWAS on AgP inside and outside Japan and a possible mechanism of the pathogenesis of AgP based on available literature and our research findings. These findings will lead to advancements in the prevention, prognosis, and treatment of AgP.

1. Introduction

The advent of next-generation sequencing technology in 2005 has dramatically affected the cost, accuracy, and utility of genome analysis. This new technology is the driving force behind the remarkable progress of research in the field of genome analysis and the opening up of new research fields, such as bioinformatics (the science of analyzing life phenomena using informatics methods) [1]. In response to this trend, genome-wide association studies (GWAS), a comprehensive genome analysis that utilizes bioinformatics, have recently become a global trend in the medical community for analyzing genomic mutations in cancers or searching for disease-related genes. By integrating the genetic results from GWAS and the clinical features of patients, "tailor-made medicine" (personalized medicine) and "precision medicine," which apply the results of genome analysis to diagnoses and treatments, can be provided to individual patients [2].

Aggressive periodontitis (AgP), Stage III or IV and Grade C in the new periodontitis classification, is characterized by rapid destruction of periodontal tissues (alveolar bone loss and loss of attachment) and familial aggregation, although patients remain generally healthy [3]. It has an early age of onset (teens to thirties), and there is little bacterial plaque in the oral cavity. The presence of intrafamilial aggregation suggests the involvement of not only environmental factors normally observed in chronic periodontitis (CP) but also genetic factors in the pathogenesis of this disease. Until now, single-nucleotide polymorphisms (SNPs) in inflammatory cytokines have been reported to be associated with this disease. However, a clear association with this disease is yet to be identified. This is because single-gene analyses have only been conducted to examine the presence or absence of known genes [4].

In recent years, several studies have applied GWAS to analyze complicated diseases, such as AgP, and have comprehensively searched for markers impacting these diseases [5]. This unbiased approach successfully identified AgP-related genes and some AgP-suggestive genes.

In this review, we introduce GWAS and the latest findings in the search for disease-associated genes using GWAS in dentistry, particularly in periodontology. In addition, we summarize the notable GWAS conducted on AgP and highlight the genetic variants that have been implicated in the disease. Furthermore, we discuss the biological functions associated with the identified genetic variants and their potential

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relevance to AgP pathogenesis. Finally, we discuss the limitations of GWAS and current challenges in the construction of a large Japanese AgP database.

2. Genetic polymorphisms

Genetic polymorphisms play an important role in the development of hereditary diseases. These diseases can arise from two scenarios: transmission of genetic mutations from parents to children, or mutations occurring in genes and chromosomes that lead to diseases such as cancer, even when the parents themselves do not possess any mutations. Unlike diseases caused by a single gene, such as hemophilia and rickets, common diseases (lifestyle diseases such as diabetes, hypertension, and periodontitis) are influenced by the combined effects of polymorphisms in multiple disease-related genes and environmental factors.

SNPs are genetic polymorphisms with diverse single-nucleotide variations found in the genome sequence, and approximately 3–10 million SNPs are present throughout the genome [6]. A mutation in a single nucleotide can lead to changes in protein structure, expression, and function, resulting in genetic "individual differences." For example, SNPs in the gene encoding alcohol dehydrogenase (*ALDH2: Aldehyde Dehydrogenase*), an enzyme that breaks down aldehydes, are associated with alcohol sensitivity [7].

Numerous studies have explored the relationship between SNPs and "susceptibility to various diseases." GWAS are instrumental in identifying disease-related variants in various diseases. For example, a GWAS was conducted on type 2 diabetes (T2D), involving 180,834 T2D patients and 1159,055 controls and identified 237 T2D-related loci that were significantly different ($P < 5 \times 10^{-9}$) from those of controls [8]. Not all of these genes are necessarily detected in patients with T2D, because genetic susceptibility is just one of many factors influencing common diseases such as T2D, and other environmental and behavioral factors also play a significant role in the development and progression of this disease [9]. Despite the large number of variants discovered using GWAS across different studies, there has been no overlap in genes identified, because the associated variants explain only a small proportion of the heritability of T2D [10,11]. Therefore, it is essential to accumulate the results from large-scale GWAS to identify risk variants of complex diseases.

3. GWAS in dental fields

GWAS have significantly contributed to advancing our understanding of the genetic background of complex diseases, including dental diseases. A GWAS is a powerful method for investigating the association between genetic variations across the entire genome and specific traits or diseases. In dental studies, GWAS have been employed to identify genetic factors associated with various oral health conditions and traits [12]. These conditions include periodontal disease [13–20], dental caries [21–27], dental abnormalities [25,28–30], and craniofacial abnormalities [31–36]. By analyzing a large cohort of individuals, GWAS can identify common genetic variants, including SNPs that are significantly associated with the risk or susceptibility to the dental diseases. These studies have shed light on the complex interplay between genetic and environmental factors in the development of oral health conditions.

GWAS findings in dental research have not only identified specific genetic loci associated with dental diseases but also provided insights into the underlying biological mechanisms involved. These discoveries have contributed to a better understanding of the disease pathways and potential therapeutic targets. Additionally, GWAS in dental studies have facilitated the development of genetic risk predictions. By combining information from multiple genetic variants, researchers have created polygenic risk scores to estimate an individual's genetic predisposition to certain dental conditions. These risk prediction models have the potential to improve personalized dental care and enable early intervention strategies.

Table 1
Chronic periodontitis (CP)-related and -suggestive genes in Japanese and non-Japanese populations.

dbSNP ID	Gene (s) or gene (s) adjacent to	P-value	Population	Disease severity	Ref
rs10457525	*LAMA2*	3.5×10^{-6}	Caucasians	PD[a] at least 5.5 mm in two sextans	15
rs7749983		2.4×10^{-6}			
rs10457526		6.0×10^{-6}			
rs3870371	*HAS2*	5.6×10^{-6}			
rs11659841	*CDH2*	9.4×10^{-6}			
rs2297778	*ESR1*	9.7×10^{-6}			
rs3783412	*SOS2/NIN*	7.9×10^{-6}			
rs12630254	*OSBPL10*	6.7×10^{-6}			
rs12630931		6.2×10^{-6}			
rs733048	*HSP90AB2P*	1.0×10^{-6}			
rs12589327	*SEL1L*	6.6×10^{-6}			
rs8094794	*FHOD3*	5.9×10^{-6}			
rs149133391	Intron between *TSNAX* and *DISC1*	7.9×10^{-9}	Hispanic	Interproximal attachment loss	37
rs11800854	*KCNK1/ KIAA1804*	2.9×10^{-7}	Caucasians	Moderate and severe CP	16
rs12032672	Upstream of *PKN2*	9.6×10^{-7}			
rs10043775	*FBXO38* (missense change)/*HTR4*	2.4×10^{-6}			
rs16924631	*UHRF2* (non-coding transcript variant)/*GLDC*	3.2×10^{-6}			
rs10010758	*TBC1D1* (intron)/ *PTTG2*	3.7×10^{-6}			
rs1932040	intron between *CLIC5* and *RUNX2*	1.3×10^{-6}			
rs9942773	*CSMD3/TRPS1*	1.9×10^{-6}			
rs1616122	*CAMTA1* (intron)/ *VAMP3*	4.9×10^{-6}			
rs11621969	*FOS/ JDP2*	9.4×10^{-7}			
rs6885116	*ODZ2* (intron)	1.4×10^{-6}			
rs1970525	*GRID1*	3.8×10^{-6}			
rs11800854	*KCNK1/ KIAA1804*	4.0×10^{-6}			
rs9287989	*KIAA1715/ EVX2*	4.4×10^{-6}			
rs9446777	*KCNQ5*	4.8×10^{-6}	Japanese	PD[a] at least 4 mm	18
rs2392510	*GPR14* (intron)/ *NME8*	4.2×10^{-6}			

The variants associated with CP were listed.
[a] PD: pocket depth

4. GWAS in periodontology

GWAS on periodontitis have made significant contributions to our understanding of the genetic factors associated with this condition. Periodontitis is a complex inflammatory disease that affects the supporting structures of the teeth, including the gingiva, periodontal ligament (PDL), and alveolar bone. These factors are influenced by a combination of genetic, environmental, and lifestyle-related factors. A GWAS involves scanning the entire genome of individuals to identify genetic variations associated with a particular disease or trait. In the context of periodontitis, GWAS have helped to identify specific genetic loci or regions associated with an increased risk of developing the disease or influencing its severity.

Several GWAS have been conducted in the field of periodontology and have revealed a number of genetic variants associated with chronic periodontitis (CP) (Table 1). These studies have provided insights into the biological pathways and processes involved in the development of periodontitis and have identified potential therapeutic targets. Shaffer et al. conducted a GWAS on young non-Hispanic American Caucasians. They identified suggestive loci in CP ($P < 1.0 \times 10^{-5}$) such as *Laminin Subunit Alpha 2* (*LAMA2*), *Hyaluronan Synthase 2* (*HAS2*), *Cadherin 2* (*CDH2*), *Estrogen Receptor 1* (*ESR1*), *SOS Ras/Rho Guanine Nucleotide Exchange Factor 2* (*SOS2*), and *Ninein* (*NIN*) that have been previously reported as the periodontitis-association genes and *Oxysterol Binding Protein Like 10* (*OSBPL10*), *Heat Shock Protein 90 Alpha Family Class B Member 2, Pseudogene* (*HSP90AB2P*), *SEL1L Adaptor Subunit Of ERAD E3 Ubiquitin Ligase* (*SEL1L*), and *Formin Homology 2 Domain Containing 3* (*FHOD3*) as the novel CP-related genes [15]. Sanders et al. conducted a GWAS with CP samples in the Hispanic population and identified *Transil Associated Factor X* (*TSNAX*) *-DISC1 Scaffold Protein* (*DISC1*) SNP rs149133391 as a definitive CP-related gene ($P = 7.9 \times 10^{-9}$) [37]. A replication study of the identified *TSNAX-DISCI* SNP showed significance in European-American individuals. However, this was not significant for African-Americans. Shimizu et al. performed GWAS using samples from BioBank Japan (case: 1593 and control: 7980) and identified the two CP-suggestive genes in a Japanese population: *the Potassium Voltage-Gated Channel Subfamily Q Member 5* (*KCNQ5*) SNP rs9446777 ($P = 4.83 \times 10^{-6}$) and *G Protein-Coupled Receptor 141* (*GPR141*)*-NME/NM23 Family Member 8* (*NME8*) SNP rs2392510 ($P = 4.17 \times 10^{-6}$). They performed a replication study with 1,167 cases and 7,178 controls. However, these suggestive genes showed no significance [18].

As bacteria are one of the risk factors in CP, several studies have combined the bacterial factor and genetic factor in GWAS. For example, Divaris et al. carried out a GWAS on Caucasians with CP and examined CP-related variants and their association with eight bacterial colonizations. They identified 13 CP-suggestive genes ($P < 5 \times 10^{-6}$). However, they have no association with *Aggregatibacter actinomycetemcomitans* [16]. Later, Rhodin et al. analyzed the variants related to bacterial colonization in addition to CP-related variants. They used GWAS of CP and periodontal pathogen colonization from a cohort of Americans of European descent participating in the Atherosclerosis Risk in Communities study and identified four suggestive CP-related variants with severe CP such as *NIN*, *Abhydrolase Domain Containing 12B* (*ABHD12B*), *WASP Homolog Associated With Actin, Golgi Membranes And Microtubules* (*WHAMM*), and *Adaptor Related Protein Complex 3 Subunit Beta 2* (*AP3B2*) and two suggested genes with high periodontal pathogen colonization such as *Potassium Two Pore Domain Channel Subfamily K Member* (*KCNK1*) associated with red complex and *DAB2 Interacting Protein* (*DAB2IP*) associated with *Porphyromonas gingivalis* [38]. Toyama et al. used GWAS and 16 s rRNA sequencing to identify the association between CP-related genes and periodontal microbiota using Japanese healthy and CP samples [39]. Although no CP-related SNP was identified, *Lactobacillaceae, Desulfobulbaceae* and *Porphyromonas gingivalis* were abundant in the samples from the patients with periodontitis.

In addition to these specific genetic associations, GWAS have provided insights into the shared genetic architecture of periodontitis and other related traits or diseases. For instance, genetic variants associated with periodontitis have been found to overlap with those associated with other inflammatory conditions, such as rheumatoid arthritis and Crohn's disease [40,41]. This finding suggests that shared underlying mechanisms and pathways are involved in inflammatory diseases.

Table 2
Aggressive periodontitis (AgP)-related and -suggestive genes in non-Japanese populations.

dbSNP ID	Gene(s) or gene (s) adjacent to	P-value	Population	Disease severity	Ref
rs1537415	*GLT6D1*	5.5×10^{-9}	German, Dutch	$\geq$ 50% bone loss at 2–6 teeth or $\geq$ 50% bone loss at $\geq$ 7 teeth	13
rs2978951	*DEFA1A3*	2.1×10^{-8}	German, Dutch, Turkish	$\geq$ 2 teeth with 50% alveolar bone loss	43
rs2738058		6.8×10^{-10}			
rs4284742	*SIGLEC5*	1.3×10^{-8}			
rs35709256	*FAT3* (intron)	9.5×10^{-7}	Caucasian Spanish	III/IV Grade C	47
rs4807188	*CSNK1G2* (intron)	1.8×10^{-6}			
rs2074872	*MYH13* (intron)	2.8×10^{-6}			
rs116611488	*CNTN2* (upstream)	2.9×10^{-6}			
rs4854545	*ANTXR1* (intron)	3.0×10^{-6}			
rs78672540	unknown	3.8×10^{-6}			
rs13439823	*ANGPT1* (intron)	4.2×10^{-6}			
rs11993287	*PLEC* (downstream)	4.3×10^{-6}			
rs198712	*NPY*	9.8×10^{-6}	German	$\geq$ 2 teeth with 50% alveolar bone loss	48
rs10982617	*DEC1*	6.2×10^{-7}	North West European	$\geq$ 2 teeth with 50% alveolar bone loss	50

5. Genetic polymorphism analysis of AgP

GWAS have significantly contributed to our understanding of the genetic factors associated with AgP. AgP is a severe form of periodontal disease characterized by rapid progression and early onset, and often affects young individuals [3]. The followings are some key findings from the GWAS on AgP in non-Japanese populations (Table 2). Schaefer et al. conducted a GWAS on German patients with AgP and identified a significant association between AgP and *Glycosyltransferase 6 Domain Containing 1* (*GLT6D1*) SNP rs1537415 ($P = 5.51 \times 10^{-9}$). The association of this gene was confirmed in replication study using samples from Dutch patients with AgP and fine-mapping [13]. This result was replicated in a sub-Saharan population in Sudan [42]. This gene plays a role in the binding affinity in *GATA Binding Protein 3* (*GATA3*), a transcription factor of Th2 differentiation, suggesting its involvement in the disruption of T cell differentiation and the immune response in AgP [13]. Munz et al. conducted a GWAS on German and Dutch populations, and later validated the results in Turkish patients with AgP. They identified three shared risk variants of AgP and CP: *Defensin Alpha 1 And Alpha 3, Variable Copy Number Locus* (*DEFA1A3*) SNPs rs2978951 ($P = 2.06 \times 10^{-8}$) and rs2738058 ($P = 6.78 \times 10^{-10}$), and *Sialic Acid Binding Ig Like Lectin 5* (*SIGLEC5*) SNP rs4284742 ($P = 1.34 \times 10^{-8}$) [43]. DEFA1A3 is expressed in neutrophils and macrophages and is involved in anti-microbial activity [44]. SIGLEC5 induces myeloid cell activation to prevent inappropriate reactivity against self-tissue [45]. It is also

expressed in osteoclasts and inhibits Fc epsilon receptor1 (FCεRI)-mediated activation [46]. Dysregulation of these genes may contribute to the immunodeficiency and bone loss observed in AgP [43]. de Coo et al. carried out GWAS on a Caucasian Spanish population and the pathway analysis to identify AgP-related genes. They found eight SNPs as AgP-suggestive genes ($P < 5 \times 10^{-6}$) such as rs35709256, rs4807188, rs2074872, rs116611488, rs4854545, rs78672540, rs13439823, and rs11993287 [47]. The pathway analysis enriched five pathways such as cyclic adenosine 3′, 5′-monophosphate (cAMP) medicated signaling, regulation of Interleukin-2 (IL-2) expression in activated T lymphocytes, cluster of differentiation 28 (CD28) signaling in T helper cells, Vitamin D receptor/Retinoid X Receptor Alpha (VDR/RXR) activation, and phosphatidylinositol 3′-kinase (PI3K)/Akt signaling. The identified genes are involved in immune cell function and may contribute to the dysregulation of the immune response in AgP. Two GWAS analyzed the association between AgP and sex-specific variants. Freitag-Wolf et al. conducted a GWAS using the samples from the German AgP male patients and identified *Neuropeptide Y* (*NPY*) SNP rs198712 as a suggestive AgP-variant in men ($P = 9.76 \times 10^{-6}$) [48]. It was validated by using samples from German and Australian patients with AgP. *NPY* is detected in gingival crevicular fluid and is decreased in periodontitis [49], suggesting that it is important for the maintenance of periodontal tissues and that its deficiency causes tissue destruction. Later, the same group performed a GWAS on young European women with AgP to identify female specific AgP-related genes [50]. They identified genetic loci associated with AgP. One of the identified female specific AgP-suggestive variants was *Deleted in esophageal cancer 1* (*DEC1*) SNP rs10982617 ($P = 6.2 \times 10^{-7}$), which is involved in the pathophysiology of periodontitis [51].

Historically, many GWAS have been conducted on individuals of European ancestry, leading to potential biases in the identification of genetic risk factors for this disease [52,53]. In addition to disease-related variants, different racial and ethnic groups may have distinct genetic variations that influence disease susceptibility and treatment responses [54]. Therefore, AgP-related SNPs identified in European populations are not necessarily true in the Japanese population. By including diverse populations in a GWAS, researchers can identify population-specific genetic variations related to periodontitis. This approach improves our understanding of the genetic architecture of this disease and enables the development of personalized treatment strategies. However, a few GWAS have been conducted on AgP in Asian populations, including the Japanese population, and definitive AgP-related genes have not yet been identified.

6. History to identify the disease-related genes of AgP in Japan

The association between AgP and haplotypes of the human leukocyte antigen (HLA) has been intensively studied in Japan [55,56]. HLA haplotypes are genetic markers that play a role in antigen recognition on antigen-presenting cells and determine immune responses. Several genotyping studies have explored potential haplotypes of AgP. For example, Ohyama et al. revealed that DRB1 * 1501, DRB1 * 1401, DQB1 * 0602, and DQB1 * 0503 genotypes were frequently detected in Japanese patients with AgP, whereas DRB1 * 0405 and DQB1 * 0401 were less frequently detected [57]. However, the strong correlation between HLA haplotypes and AgP remains controversial [58]. Further research with larger sample sizes is warranted to establish a conclusive relationship between AgP and specific HLA haplotypes.

It has been reported that the patients with periodontitis have an antigen, Ag53, that is detected on the vesicle surface of *Porphyromonas gingivalis* 381 [59]. Ohyama et al. reported that Ag53 evokes a strong humoral immune response in patients with AgP because T cells carrying the HLA-DRB1 * 1501-DQB1 * 0602 and/or DRB1 * 1401-DQB1 * 0503 haplotypes respond to Ag53 and proliferate [60].

Table 3
Aggressive periodontitis (AgP)-related genes in Japanese populations.

dbSNP ID	Gene (s)	Major allele	Minor allele	Position (bp)	Sample number of AgP	Ref
NA[a]	*MMD2*	C	T	347	N = 6 from 1 family	61
rs571102620	*NOD2*	G	A	328	N = 5 from 2 families	62, 65
rs104895427		C	T	931	N = 101 (unrelated)	
rs1078327		C	T	1411		
rs143793106	*LIPA*	T	C	1009	N = 44 (unrelated)	68

The variants confirmed by the replication studies or functional analyses were listed as AgP-related genes.
[a] NA: no information in the reference

7. Identification of disease-related genes of Japanese AgP by GWAS

In recent years, GWAS of AgP in Japan have provided valuable insights into the genetic factors associated with this disease in the Japanese population. The key findings of the GWAS conducted in Japan are represented (Table 3):

7.1. A SNP in Monocyte to macrophage differentiation associated 2 (MMD2)

Mizuno et al. searched for genes associated with AgP using samples from patients with AgP and healthy individuals from single family line [61]. Exome sequencing analysis was performed on six patients with AgP and four healthy individuals without AgP in the three generations of a family as controls. They identified an SNP in the *MMD2* gene as an AgP-related gene (Fig. 1A). The functional analyses of *MMD2* wild-type (WT) and its SNP in vivo suggest that deletion or mutation of the gene affects neutrophil migration and decreases its number, resulting in an inability to defend against bacterial infection. These results suggested that *MMD2* is involved in the onset and progression of AgP.

7.2. SNPs in Nucleotide binding oligomerization domain containing 2 (NOD2)

Sudo et al. conducted a GWAS on two Japanese families of patients with AgP and searched for variants associated with AgP [62]. They performed exome sequencing analysis on two Japanese families, one consisting of three patients with AgP and one healthy person in the three generations of a family (Family 1), and the other consisting of two siblings with AgP in a family (Family 2). The results of exome sequencing analysis showed that 74,615 AgP-related candidate genes were detected in family 1 and 59,949 candidate genes were detected in family 2. These genes were filtered using the following criteria: (1) genes with a depth of 10 or greater, (2) genes that were not deletions or insertions, (3) genes that were linked to disease, (4) genes that were missense variants, and (5) genes with a minor allele frequency (MAF) of < 1% compared to the database of healthy individuals. There were 96 AgP-related candidate genes in family 1 and 321 candidate genes in family 2. Furthermore, two *NOD2* SNPs (rs199858111 and rs765857594) were identified as AgP-related genes after confirmation by Sanger sequencing (Fig. 1B). Targeted sequencing analysis of *NOD2* SNPs in 94 unrelated Japanese patients with AgP revealed that two patients harbored these SNPs. *NOD2* is detected in mononuclear cells and fibroblasts in lesions with inflammatory cell infiltration in patients with periodontitis [63]. Moreover, it recognizes periodontal pathogens by its pattern recognition receptor and promotes nuclear factor κB, thereby inducing an innate immune response [64].

Mizuno et al. also detected two variants of *NOD2* by GWAS with

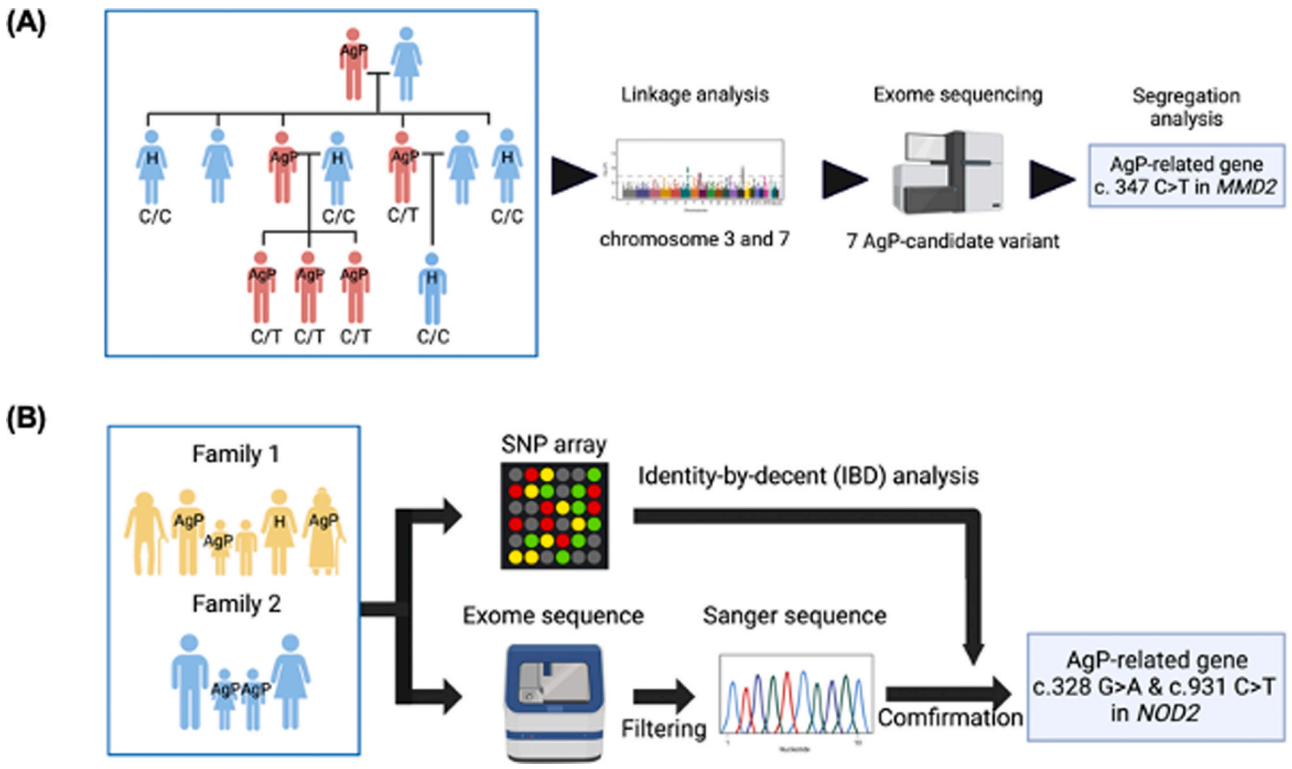

Fig. 1. The experimental flows to identify AgP-related genes in Japanese families. (A) The experimental flow to detect AgP-related gene, c. 347 C>T in *MMD2*. (B) The experimental flow to detect AgP-related genes, c. 328 G>A & c .931 C>T in *NOD2*. AgP: patients with aggressive periodontitis, H: healthy individual without periodontitis.

samples from different AgP patients (a total of 101 AgP patients: 37 patients with positive family histories and 64 sporadic AgP patients) [65]. Interestingly, one of them, *NOD2* rs104895427c .931 C>T was commonly identified as a Japanese AgP-related suggestive variant in both GWAS. Further functional analyses of the SNPs identified in *NOD2* are warranted to elucidate the pathogenesis of AgP.

7.3. SNPs affecting the cytodifferentiation of PDL cells

We searched for disease-related genes in Japanese patients with AgP using exome sequencing. Forty-four patients diagnosed with AgP were included in this study. Exome sequencing was performed using DNA extracted from the peripheral blood of patients with AgP. An average of 74,677 SNPs were obtained per patient. To analyze the exome sequencing data of Japanese patients with AgP, the following screening was performed to search for disease-related genes: (1) MAF must be less than 5% in the 1000 Genomes Database, (2) depth must be $\geq$10, (3) SNPs must be detected in four or more patients, and (4) SNPs cause mutations and affect its protein functions and structure. The Japanese Gene Reference Database from the *iJGVD,* a gene reference library database for healthy Japanese individuals, was used as a control group [66]. By comparing the control and AgP data, several genes with statistically significant differences ($P < 0.05$) in the expression frequency of SNPs were identified as candidate disease-related genes. One of these candidate genes was *Lipase A, Lysosomal Acid Type* (*LIPA*) (rs143793106), which encodes lysosomal acid lipase (LAL) that catalyzes the hydrolysis of cholesteryl esters and triglycerides in lysosomes, thereby producing cholesterol, free fatty acids, and glycerol. The MAF of *LIPA* SNP rs143793106 in the AgP group was 4.55%, whereas that of the control group was 1.66% ($P = 3.7 \times 10^{-2}$; odds ratio, 2.82; 95% confidence interval, 1.02–7.81). Loss-of-function mutations in the *LIPA* gene cause Wolman's disease, a rare genetic disease characterized by abdominal distention, hepatosplenomegaly, and adrenal calcification. Additionally, *LIPA* has been reported as an atherosclerosis-related gene associated with ectopic calcification in sclerotic lesions [67]. Based on these studies, we presumed that *LIPA* is associated with calcification in the periodontal tissue. We analyzed the function of *LIPA* during the differentiation of PDL cells into hard tissue-forming cells and found that while *Alkaline phosphatase* and *Type I collagen*, which are calcification-related genes, were normally expressed in WT *LIPA*-expressing PDL cells, *LIPA* SNP rs143793106 and the expression of these calcification-related genes were lower in PDL cells. Specifically, WT *LIPA* carriers can maintain periodontal tissue homeostasis by inducing normal differentiation of PDL cells. In contrast, suppression of PDL cell differentiation in *LIPA* SNP rs143793106 carriers may facilitate the disruption of periodontal homeostasis, leading to an early onset of AgP [68].

These studies highlight the importance of genetic variations in immune-related genes and cellular processes, including cytodifferentiation of PDL cells, in the onset and progression of AgP in the Japanese population. These findings provide valuable insights into the mechanisms underlying this disease and identify potential targets for future research and therapeutic interventions.

8. Mechanisms of *LIPA* SNP rs143793106 induce AgP pathogenesis

Interestingly, the identified SNPs as AgP-related genes, such as *G Protein-Coupled Receptor 126* (*GPR126*) (rs536714306) [69], *Sphingomyelin Phosphodiesterase 3* (*SMPD3*) (rs145616324) [70], *Paraoxonase 1* (*PON-1*) (rs854560) [71], and *LIPA* (rs143793106) [68], from our AgP samples were all associated with energy metabolism, especially lipid metabolism. Interestingly, Hong et al. conducted a GWAS on CP in a Korean population and identified two suggestive genes related to lipid-metabolism [72]. Based on these findings, we hypothesized that lipid metabolism disorders are involved in the pathogenesis of periodontitis. Therefore, we analyzed the mechanisms underlying the pathogenesis of AgP in a representative AgP-related gene, *LIPA*, in terms

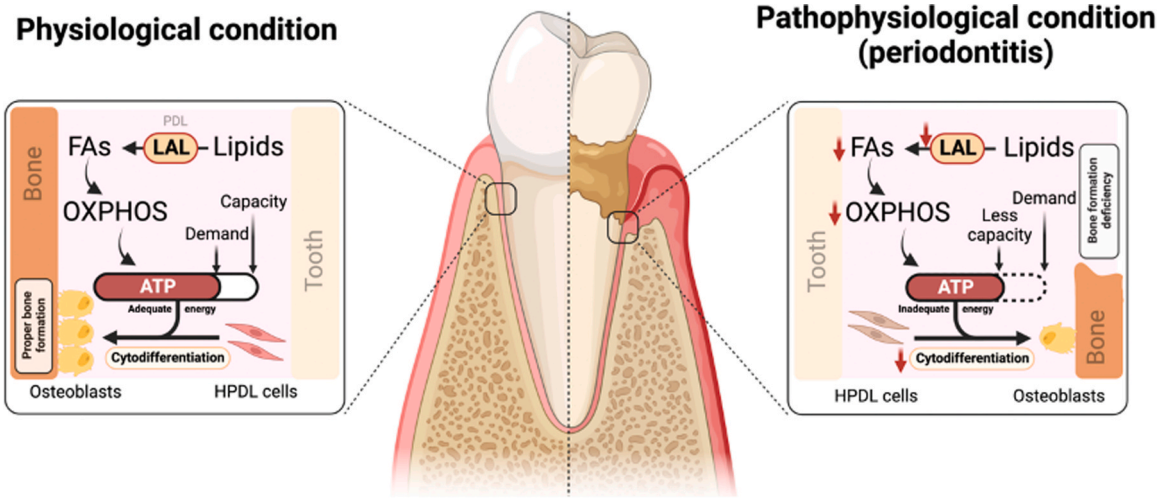

Fig. 2. The mechanism of the decreased LAL function in the pathogenesis of AgP. LAL supports OXPHOS to generate adequate ATP demanded during PDL cytodifferentiation in the homeostasis. In contrast, decreased or impaired LAL function reduces the amount of FAs and OXPHOS ability, resulting in inadequate energy to sustain the ATP production required for PDL cytodifferentiation.

of energy metabolism.

LIPA-encoding LAL catalyzes the hydrolysis of lipids such as cholesteryl esters and triglycerides in lysosomes, thereby producing fatty acids (FAs) [73]. FAs are utilized to generate adenosine triphosphate (ATP), which is the primary energy source for cellular processes, via oxidative phosphorylation (OXPHOS) in mitochondria. *LIPA* SNP rs143793106 reduces the intracellular and extracellular enzyme activities of LAL by approximately 33% and 16%, respectively. Inhibition of LAL decreases lipid droplet utilization by the mitochondria in PDL cells and the spare capacity of the mitochondria, resulting in reduced ATP production via the OXPHOS pathway, which is the principal energy pathway during the cytodifferentiation of PDL cells. These findings indicate that under physiological conditions, owing to normal LAL function, PDL cells acquire the necessary energy for their cytodifferentiation through lipid metabolism, which maintains and enhances mitochondrial function and drives OXPHOS, leading to the homeostasis of the periodontal tissue. In contrast, in AgP, owing to a defect in the LAL function, ATP production via OXPHOS is reduced because of fewer FAs and mitochondrial dysfunction in PDL cells. An inadequate amount of ATP may not support PDL differentiation, resulting in rapid destruction of periodontal tissue (Fig. 2) [74]. These findings revealed the importance of lipid metabolism in providing the energy required for the differentiation of PDL cells and the involvement of energy metabolism in AgP pathogenesis.

9. Limitations of GWAS

As described in this review, the causative genes involved in AgP pathogenesis have been identified using GWAS. However, GWAS requires a large number of specimens, as the significance level of MAF between the control and disease groups is usually set at 5×10^{-7} to 5×10^{-8} [16,75–77]. In general, the incidence rate of AgP is 0.1–0.2% in Caucasians, 1.0–3.0% in African Americans, and 0.5–1.0% in Hispanics [78], while that in Japanese ranges from 0.03% to 0.47% [79,80]. Therefore, it was difficult to collect sufficient samples for statistical analysis. Several countries conducted collaborative studies to address this issue. For example, in Europe, German and Dutch groups collaborated and established a large-scale AgP database including nearly 1000 cases: German AgP samples from the German biobank Popgen [81] and Dutch AgP samples from the Academisch Centrum Tandheelkunde Amsterdam (ACTA). In Japan, the Japanese Society of Periodontology (JSP) has led a collaborative clinical study with 12 dental schools nationwide to increase the sample size of Japanese AgP and construct a larger database of AgP in the Japanese population. In addition, JSP charges BioBank for Japanese AgP samples. The collected samples from patients with AgP were stored in the Biobank and are available for researchers interested in genetic studies of AgP. Accordingly, JSP plays an important role in collaborating, facilitating data sharing, and accelerating research progress.

10. Future prospects

In this review, we focused on GWAS, particularly on AgP. This allowed us to better understand the genetic predisposition to AgP. In addition, the exploration of other omics analyses is necessary to unravel the complex mechanisms of periodontal tissue destruction. Various relevant omics technologies include transcriptomics, proteomics, and metabolomics [82–85]. The integration of multiple omics datasets, including data obtained from GWAS, can provide a more comprehensive understanding of the disease. Trans-omics analyses enable us to decipher the intricate interplay between genetic and environmental factors, including bacterial factors, which will shed light on novel avenues for therapeutic interventions and personalized treatment approaches [86–88]. For example, mathematical modeling is a complementary tool for studying the pathogenesis of periodontitis. It allows the simulation of disease progression, assessment of treatment outcomes, and prediction of the impact of genetic variation on disease susceptibility.

Recently, we combined multi-omics and mathematical modeling to establish a data-driven *in silico* model of periodontitis. Using this model, we elucidated the causal factors of the disease at the systemic level. This model enables the identification of disease-specific combination biomarkers, novel drug discovery, and *in silico* individual treatment planning. Similarly, future research in periodontology to realize personalized medicine requires interdisciplinary collaboration between mathematicians and periodontal researchers to harness the full potential of big data from omics analyses. The establishment of disease-specific omics databases through comprehensive data collection and analysis is important for advancing the field of periodontology.

11. Conclusion

GWAS in periodontology have provided valuable insights into the genetic basis of AgP, identified potential therapeutic targets, and contributed to our understanding of the shared genetic architecture between periodontitis and other inflammatory conditions and AgP-specific pathogenesis. Despite its limitations, GWAS is a powerful tool

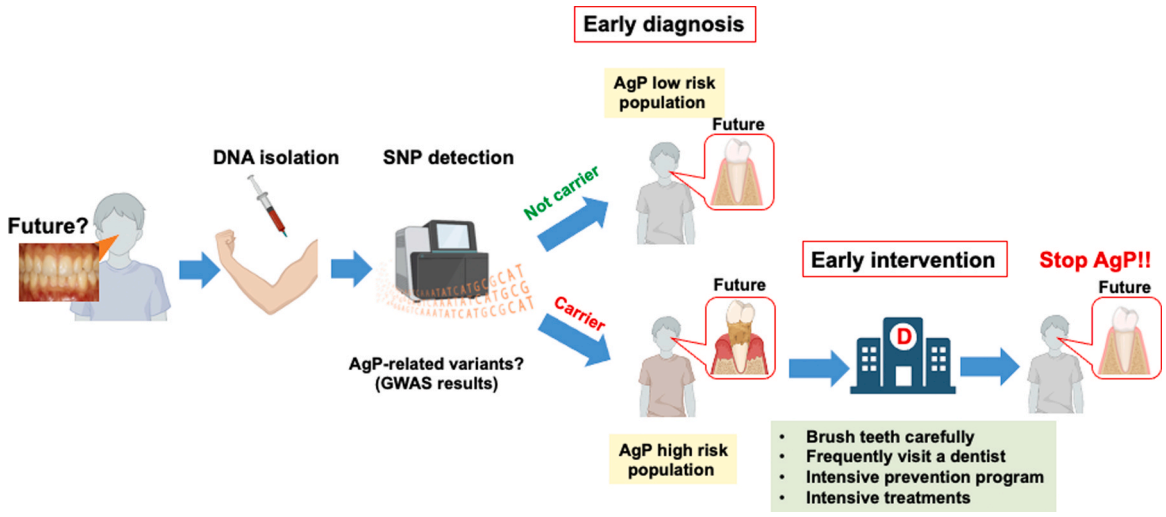

Fig. 3. The prospect of GWAS results in stopping the deterioration of AgP.

for identifying genetic loci and pathways associated with AgP, providing important insights into the etiology of this disease and potential therapeutic targets. In the future, the AgP-related variants identified from the GWAS will be used as markers for the early diagnosis of AgP, which will allow us to provide prevention or early intervention for patients with AgP (Fig. 3). We hope that this would ultimately stop the onset and progression of AgP.

Conflict of Interest

The authors declared no potential conflicts of interest for the research, authorship, and/or publication of this article.

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