BMC Oral Health

RESEARCH Open Access

Genome-wide association meta-analysis identifies two novel loci associated with dental caries

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Abstract

Background Tooth loss significantly impacts oral function and overall health deterioration. Dental caries and periodontal disease are major contributors to tooth loss, emphasizing the critical need to prevent these conditions. Genetic studies have played a crucial role in deepening our understanding of the underlying mechanisms of these diseases. While large-scale genome-wide association studies (GWAS) on dental caries and periodontal disease have been conducted extensively, research focusing on Asian populations remains limited. Given substantial genetic and lifestyle variations across ethnicities, conducting studies across diverse populations is imperative. This study aimed to uncover new insights into the genetic mechanisms of these diseases, contributing to broader knowledge and potential targeted interventions.

Methods We conducted a GWAS using genome data from 45,525 Japanese individuals, assessing their self-reported history of dental caries and periodontal disease. Additionally, we performed a meta-analysis by integrating our results with those from a previous large-scale GWAS predominantly involving European populations.

Results While no new loci associated with periodontal disease were identified, we discovered two novel loci associated with dental caries. The lead variants of these loci were intron variant rs10974056 in *GLIS3* and intron variant rs4801882 in *SIGLEC5*.

Conclusion Our study findings are anticipated to advance understanding of the underlying mechanisms of dental caries and periodontal disease. Thes insights may inform better management strategies for patients affected by these conditions.

Keywords Oral cavity, Dental caries, Periodontal disease, Genetics, Genomics, Epidemiology, Genome-wide association study

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Background

The oral cavity plays important roles in verbal and nonverbal communication, diet intake, conversation, and physical appearance. Oral functions include chewing, formation and transfer of food masses, swallowing, articulation, taste, tactile sensation, and saliva secretion, all of which are basic functions necessary for a healthy life. Undoubtedly, teeth play a crucial role in oral functions. However, a decrease in the number of remaining teeth can influence food selection behavior, often leading to the avoidance of foods that are difficult to chew. This raises the risk of developing lifestyle-related diseases and malnutrition [1, 2]. Hence, tooth loss may lead not only to a decrease in oral function but also to deterioration in general health [3, 4]. Caries and periodontal diseases are major factors responsible for tooth loss, and oral bacteria have been reported to cause these diseases (e.g., periodontal disease, *Porphyromonas gingivalis*; caries, *Streptococcus mutans*) [5, 6]. The management of periodontal disease via attempted removal of bacteria is only partially effective for periodontitis and fails in high-risk individuals [7]. Thus, it is crucial to consider the interactions among the host response, genetic and environmental factors, and microbiology. A large-scale genome-wide association study (GWAS) has been conducted on the onset of these diseases [8]. However, such studies in Asian populations are limited. Therefore, we conducted a GWAS using data from Japanese populations to obtain new insights into the mechanisms of tooth decay and periodontal disease.

Methods

Study participants

Data were sourced from Japanese direct-to-consumer (DTC) genetic testing services "Genequest ALL," "Euglena MyHealth," and "HealthData Lab," which are provided by Genequest Inc. (Tokyo, Japan), Euglena Co., Ltd. (Tokyo, Japan) and Yahoo! Japan Corporation (Tokyo, Japan), respectively. We included individuals aged ≥ 18 years who agreed to participate in the study. The participants completed online questionnaires about sociodemographic factors, lifestyle habits, and medical history.

DNA sampling, genotyping, quality control, and genotype imputation

Collection and stabilization of saliva samples were conducted utilizing either the Oragene DNA Collection Kit (DNA Genotek Inc., Ottawa, Ontario, Canada) or GeneFix Saliva DNA Collection Kit (Cell Projects Ltd., Harrietsham, Kent, UK). Genotyping was executed employing various Illumina Infinium BeadChips: Global Screening Array v1 + Custom BeadChip (Illumina, San Diego, CA, USA), which contains 704,589 markers; Global Screening Array-24 v3.0 + Custom BeadChip, which contains 655,471 markers; HumanCore-12 + Custom BeadChip, which contains 302,073 markers; HumanCore-24 + Custom BeadChip, which contains 309,725 markers; and InfiniumCore-24 + Custom BeadChip, which contains 308,500 markers. Participants were divided into two groups based on the chip used because of the differences in the marker sets across these genotyping chips. Population A used the Global Screening Array v1 + and Global Screening Array-24 v3.0 + Custom BeadChips (595,105 common markers), while population B utilized the HumanCore-12+, HumanCore-24 + and InfiniumCore-24 + Custom BeadChips (289,930 common markers). Quality control and association analysis were conducted separately for each cohort.

The quality control criteria for variant filtering included: call rate per variant < 0.95, Hardy–Weinberg equilibrium exact test p-value $< 1 \times 10^{-6}$, minor allele frequency < 0.01, and exclusion of variants not located on autosomes. For participant filtering, criteria included: inconsistent sex information between the genotype and the questionnaire, call rate per subject < 0.95, closely related pairs identified via the identity-by-descent method (PI_HAT > 0.1875), and estimated non-Japanese ancestry. Quality control analyses were performed using PLINK [9, 10] (version 1.90b3.42) and Eigensoft [11] (version 6.1.3) software. To predict non-Japanese ancestry, a principal component analysis (PCA) was conducted using genomic data of African (YRI), European (CEU), Chinese (CHB), and Japanese (JPT) populations from the International HapMap Project [12]. The data were then visualized through PCA plots, and only data belonging to the Japanese cluster were used for further analyses.

For genome-wide genotype imputation, a pre-phasing/imputation stepwise approach was applied using EAGLE2 [13] (version 2.4) and Minimac3 [14] (version 2.0.1). The imputation reference panel was 1000 Genomes Phase 3 [15] (version 5). Variants demonstrating low imputation quality ($R^2 < 0.3$) and minor allele frequency (< 0.01) were excluded from further analyses. Finally, we used dosage data for 8,306,085 variants for the following GWAS.

Phenotype measurement

Phenotype data on sociodemographic factors, lifestyle habits, and medical history were collected from study participants via online questionnaires. These questionnaires included a list of medical conditions and diseases, asking participants to indicate any they currently have or have had in the past. The individuals who checked for "dental caries" were treated as cases, whereas those who did not check for "dental caries" were treated as controls. Similarly, those who checked for "periodontal disease" were treated as cases, and those who did not check for "periodontal disease" were treated as controls.

Genome-wide association and meta-analysis

We examined the associations between genetic variant dosages and the prevalence of dental caries and periodontal disease using a logistic regression model, assuming additive genetic effects. For each population, a genome-wide association study (GWAS) was conducted with adjustments for age, sex, and the first five principal components using PLINK (version 2.00a3). We combined the statistical data from both populations using a fixed-effects model and the inverse-variance weighting method with METAL software [16] (version 2011-03-25).

Genomic heritability was estimated from the GWAS summary statistics using LD Score Regression (LDSC) [17]. The analysis utilized LD score and weight files from the 1000 Genomes Phase 3 East Asian (EAS) population reference. To identify genes significantly associated with the phenotypes, we conducted a gene-based association analysis using MAGMA (Multi-marker Analysis of GenoMic Annotation) [18]. The GWAS summary statistics were annotated with gene information from the GENCODE v19 reference genome [19]. Genes identified with *p*-value less than 0.001 in the MAGMA analysis were further analyzed for functional annotation and pathway enrichment using Metascape [20].

Additionally, we conducted a meta-analysis with GWAS summary statistics from a previously reported study [8] using a *p*-value based and sample-size weighting method with the METAL software [16]. We considered the sum of Decayed, Missing, and Filled tooth surfaces (DMFS) and dentures in the previously reported study as indicators of dental caries, whereas periodontitis and loose teeth in the pre-reported study were considered as indicators of periodontal disease. The previous study utilized data from the Gene-Lifestyle Interactions in Dental Endpoints (GLIDE) consortium, UK Biobank (UKB), and BioBank Japan (BBJ). In the GLIDE and BBJ datasets, phenotypes were assessed by trained assessors or dental professionals, while in the UKB dataset, phenotypes were self-reported. Dental caries in GLIDE were evaluated using the DMFS index, resulting in continuous data with a sample size of 26,792. For periodontal disease in GLIDE, there were 17,353 cases and 28,210 controls. In UKB, there were 77,714 cases and 383,317 controls for dental caries, and 18,979 cases and 442,052 controls for periodontal disease. The BBJ dataset did not include dental caries data, but it included 3,219 cases and 209,234 controls for periodontal disease.

The significance threshold in the GWAS was set at a genome-wide significance level of $p<5\times10^{-8}$ to account for multiple testing. For newly identified loci, region plots were generated using LocusZoom.

Table 1 Characteristics of the study participants

	Case	Control
Dental caries		
N	30,859	14,666
Female (%)	47.4	38.0
Age, years (mean ± SD)	50.4 ± 12.4	48.1 ± 13.3
Periodontal disease		
N	7,059	38,466
Female (%)	44.9	44.3
Age, years (mean ± SD)	55.1 ± 12.0	48.6 ± 12.6

SD, standard deviation

Results

Genome-wide association analysis of dental caries and periodontal disease

The characteristics of the participants are presented in Table 1 and S1. This study included 30,859 cases and 14,666 controls for dental caries and 7,059 cases and 38,466 controls for periodontal disease. The number of females in the dental caries group was higher than that in the control group. The proportions of cases of dental caries and periodontal diseases by age group are presented in Table S2. Compared to the 2022 dental survey [21] results in Japan, where over 90% of individuals aged over 30 had experienced dental caries, our study indicates a prevalence of around 70%. Similarly, for periodontal disease, previous surveys reported that over 50% of older age groups were affected, whereas our study indicates a prevalence of about 30%. This discrepancy may be due to the fact that the previous survey involved examinations by dental professionals, whereas our current survey relied on self-reports, potentially leading to an underestimation of cases.

We performed a GWAS for each population and a meta-analysis of dental caries and periodontal disease (Figure S1-S6). We identified several associated loci at the genome-wide suggestive level (p-value$<1\times10^{-5}$), as shown in Tables S3 and S4. However, no associated loci were found at the genome-wide significance level (p-value$<5\times10^{-8}$). The top-associated variants were rs140784657 in the intergenic region for dental caries and rs12624579 in the *SYNDIG1* intron for periodontal disease. All 47 lead variants significantly associated with dental caries in a pre-reported GWAS [8] showed p-values>0.05 in our study (Table S5). This discrepancy could be attributed to the smaller sample size in our study and the frequency differences between European and Japanese populations. Similarly, the previously significant intron variant rs12461706 in the *SIGLEC5* gene, associated with periodontal disease in the same GWAS [8], was not significant in our study (p-value$=0.466$, Table S6). One possible reason for this is the considerable frequency difference of rs12461706 between European and Japanese populations (0.40 and 0.062, respectively).

We estimated the SNP-based heritability (h^2) of our phenotypes from the GWAS summary statistics

using linkage-disequilibrium score regression (LDSR) [17]. The total observed-scale heritability was found to be $h^2=0.0258\pm0.0155$ for dental caries and $h^2=0.0519\pm0.0182$ for periodontal disease. We conducted a gene-based association analysis using MAGMA [18] (Table S7 and S8). In the gene-based test, only the association between *ADGRL2* and dental caries had a q-value of false discovery rate (FDR) < 0.05. Genes with *p*-values < 0.001 in the MAGMA analysis were further examined using Metascape [20] for functional annotation and pathway enrichment. Functional annotation revealed several enriched biological processes and pathways (refer to Table S9 and S10).

Subsequently, a meta-analysis was performed using GWAS summary statistics from both our study and a pre-reported study [8]. We identified two novel loci associated with dental caries (Figs. 1a and 2a and b; Table 2 and S11). The lead variants of the associated loci were intron variant rs10974056 in GLI-Similar 3 (*GLIS3*) and intron variant rs4801882 in Sialic Acid-Binding Immunoglobulin-Type Lectin 5 (*SIGLEC5*). However, for periodontal disease, only previously known associated loci were identified (Fig. 1b, Table S12). The locus associated with periodontal disease on chromosome 19 was not replicated in the Japanese population (our study and Biobank Japan (BBJ) in the previously reported study). This

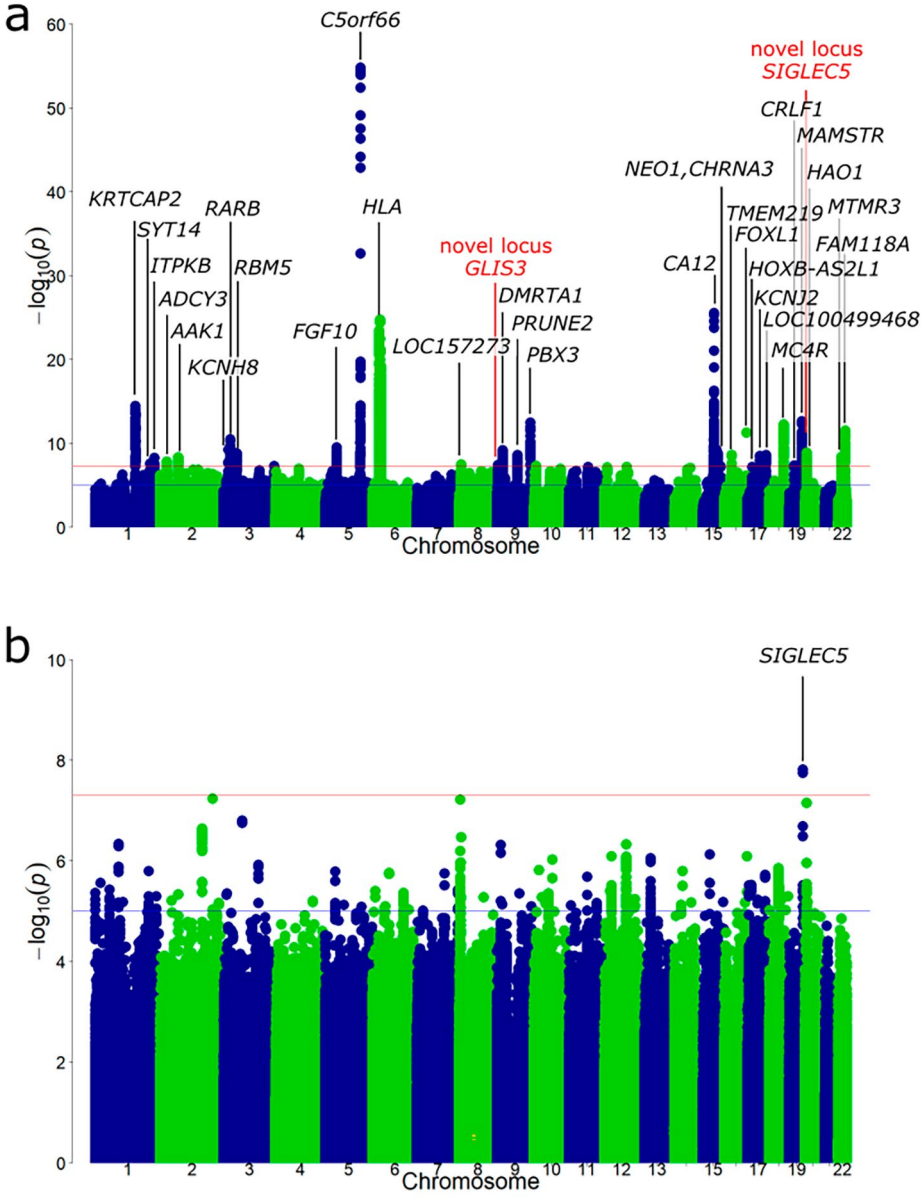

Fig. 1 Manhattan plots of the meta-analysis of dental caries (**a**) and periodontal disease (**b**)

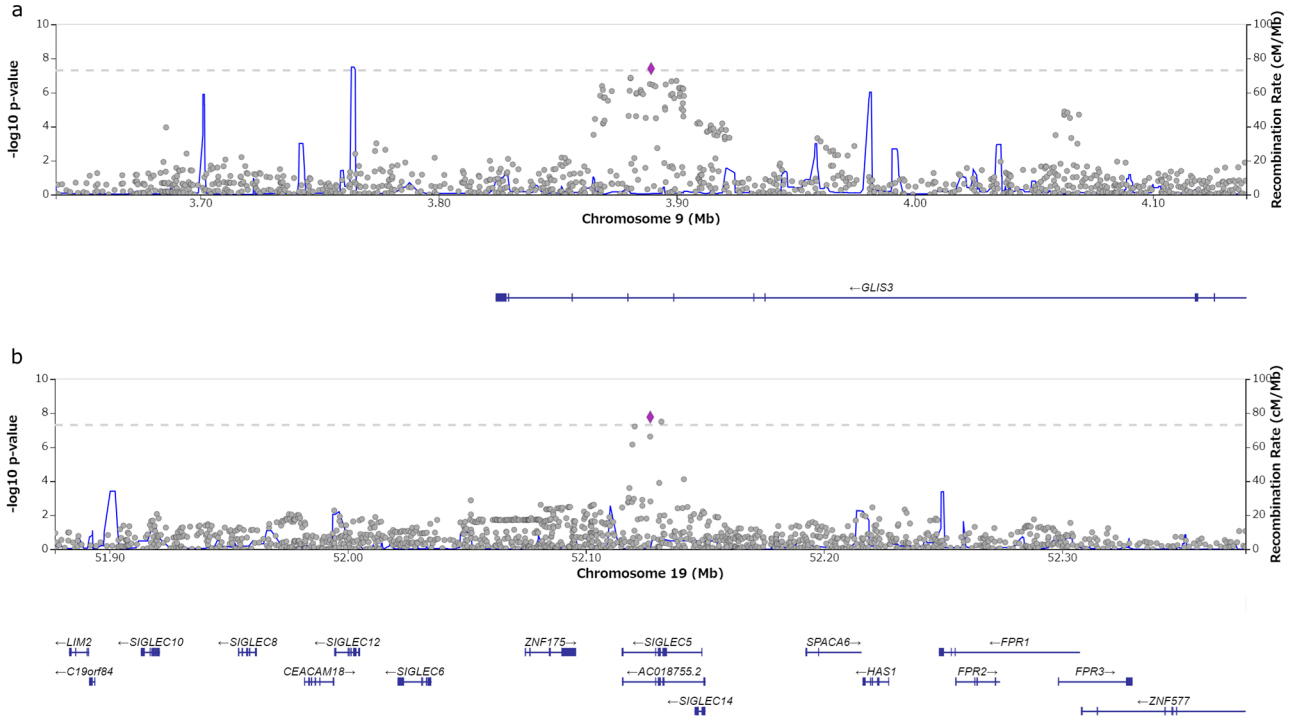

Fig. 2 Region plots of rs10974056 (**a**) and rs4801882 (**b**) for the meta-analysis of dental caries

indicates that this locus may only be associated with periodontal disease in European populations.

Discussion

In GWAS of dental caries in the present study, no loci reached the genome-wide significance level; however, through a meta-analysis of past large-scale studies, we identified two novel loci associated with dental caries. The lead variants of the associated loci were intron variant rs10974056 in *GLIS3* and intron variant rs4801882 in *SIGLEC5*. Glis3 protein, a Krüppel-like zinc finger transcription factor, plays a critical role in the regulation of pancreatic β-cell development and insulin gene expression in mice [22]. In humans, *GLIS3* gene polymorphism is associated with diabetes [23]; additionally, diabetes can increase the risk of developing dental caries and periodontal disease owing to reduced salivary secretion [24]. *GLIS3* expression has been reported to be associated with dental anomalies, although not statistically significant[25]. Therefore, the association between *GLIS3* and dental caries identified in this study can be considered robust. SIGLEC5 is a protein expressed on the surface of leukocytes that recognizes glycans containing sialic acid, playing a role in suppressing immune response [26]. Research indicates that bacteria with sialic glycans can bind to SIGLEC5, potentially evading immune response [27]. *SIGLEC5* gene polymorphisms have been associated with periodontitis in both European and East Asian populations in previous studies[28,29]. R. Mueller et al. suggested that intron variants in *SIGLEC5* gene influence its expression [30]. We identified a novel locus associated with dental caries, specifically intron variant rs4801882 in *SIGLEC5*. This SNP is also associated with periodontal disease (see Table S5). Considering this information, rs4801882 may influence the expression level of SIGLEC5 protein, potentially disrupting the oral bacterial ecosystem and affecting the survival of bacteria with sialic acid.

For periodontal disease, we were unable to identify any novel loci, and only one significant locus was not replicated in the Japanese population. However, previous studies have reported that the heritability of periodontitis is approximately 50%[31,32]. The reasons for this discrepancy might include the small effect of a single variant, the possibility that rare variants not targeted in our study are strongly associated, genetic and environmental differences between ethnicities, and inaccuracies in self-reporting because individuals do not realize that they have periodontal diseases. Considering these possibilities, further detailed investigations are necessary to clarify the association between genetic factors and periodontal disease.

Our study had some limitations. Our phenotypic data were collected via web-based self-reports, which may be subject to recall bias. Furthermore, relying on self-reports means that the severity of symptoms was not assessed, treating both severe and mild cases equally.

Table 2 Novel loci identified through genome-wide association meta-analysis of dental caries

Variant	CHR	Position	Gene	EA	NEA	Population	EAF	BETA	SE	*P*	HetIsq	HetP
rs10974056	9	3,889,264	*GLIS3*	A	C	Present study	0.1365	-0.0593	0.0255	0.0203		
						GLIDE*	0.1645	-0.0206	0.0128	0.107		
						UKB*	NA	-0.0335	0.0071	2.22E-06		
						Meta	NA	-5.494**	NA	3.93E-08	0	0.902
rs4801882	19	52,127,053	*SIGLEC5*	G	A	Present study	0.4953	-0.0302	0.0163	0.0639		
						GLIDE*	0.5646	-0.0093	0.0088	0.287		
						UKB*	NA	-0.0291	0.0055	1.49E-07		
						meta	NA	-5.639**	NA	1.71E-08	0	0.830

Loci that reached $p < 1E\text{-}6$ after meta-analysis. CHR, chromosome; EA, effect allele; NEA, non-effect allele; EAF, effect allele frequency; BETA, coefficient of effect allele; SE, standard error for beta of effect allele; P, *p*-value; HetIsq, Isq of heterogeneity; HetP, *p*-value of heterogeneity

* Gene-Lifestyle Interactions in Dental Endpoints (GLIDE) and UK Biobank (UKB) indicate the cohort of a pre-reported study[8]. ** The value of BETA column in meta-analysis indicates the Z-score

Conclusion

We identified two novel loci associated with dental caries: the lead variants were intron variant rs10974056 in *GLIS3* and intron variant rs4801882 in *SIGLEC5*. However, we did not identify any novel loci for periodontal disease, and only one significant locus did not replicate in the Japanese population. These findings are expected to contribute to understanding the mechanisms underlying dental caries and periodontal disease.

Abbreviations

BBJ	Biobank Japan
DMFS	Decayed, Missing, and Filled tooth surfaces
DTC	direct-to-consumer
GLIDE	Gene-Lifestyle Interactions in Dental Endpoints
GWAS	genome-wide association study
UKB	UK Biobank

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-024-04799-1.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

We are grateful to "Genequest ALL" and "Euglena MyHealth" for their participation in this study.

Author contributions

S.N. is an employee of Genequest Inc., K.S. is a board member of Genequest Inc., S.M. is an employee of Lion Corporation. H.K. has no competing interests.

Funding

This work was supported by internal funding from the Lion Corporation.

Data availability

The published article and its additional files include all the data analyzed in this study. Summary statistics of the GWAS analyses have been deposited in Zenodo (https://doi.org/10.5281/zenodo.10906386). All other data are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Genequest Inc. (2020-1002-4).

All participants provided written informed consent for the general use of their genetic and questionnaire data for research purposes. Prior to participation, detailed objectives of the study were sent to the participants, and an additional study-specific agreement was obtained through an opt-out approach.

Consent for publication

Not applicable.

Competing interests

S.N. is an employee of Genequest Inc., K.S. is a board member of Genequest Inc., S.M. is an employee of Lion Corporation. H.K. has no competing interests.

Received: 3 April 2024 / Accepted: 23 August 2024
Published online: 27 August 2024

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