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Genetic Loci Associated With Periodontitis: The FinnGen Study Based on National Health Registers

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ABSTRACT

Aim: To perform a genome-wide association study (GWAS) for periodontitis in the FinnGen cohort, as genetic factors contribute to periodontitis.

Materials and Methods: We included nearly 250,000 Finnish individuals who had visited a dentist in the public healthcare sector for a clinical oral examination. We designed three periodontitis phenotypes based on diagnosis and procedure codes and CPI indexes in national health registers.

Results: We identified 11 independent genetic loci associated with periodontitis, among which 6 were common and novel. A locus near the *FST* gene was associated with two phenotypes, whereas other lead SNPs were located near *ARL15*, *MFHAS1*, *DEFB130A* and *APOE*. Additionally, all phenotypes in the discovery and replication cohorts were associated with genetic variations in the HLA region. Furthermore, imputed HLA allele frequencies identified independent associations between *HLA-DRB1*, *HLA-DPB1* and *HLA-DQA1* and periodontitis. Based on single-cell RNA sequencing, the expression of genes near our lead SNPs across all three phenotypes was particularly enriched in gingival cell lineages important in the pathogenesis of periodontitis. Phenotypical and genetic correlations revealed associations between periodontitis and bacterial diseases, as well as autoimmune and cardiometabolic phenotypes.

Conclusions: Our GWAS suggests that genetic variation contributing to immune dysregulation is involved in the pathogenesis of periodontitis, which has considerable genetic similarity with other complex traits.

The members of FinnGen are listed in Supporting Information: FinnGen Author Banner.

1 | Introduction

Periodontitis is a chronic inflammatory disease driven by dysbiotic periodontal microbiota. Heritability estimates of adult periodontitis are approximately 0.34–0.38 based on twin studies and 0.01–0.24 according to genome-wide association (GWA) studies (Nibali et al. 2019; Shungin et al. 2019; Feng et al. 2014). The first GWAS of periodontitis identified an association between aggressive periodontitis and polymorphisms in glycosyltransferase (*GLT6D1*) locus (Schaefer et al. 2010); a GWAS of chronic periodontitis found an association with variants in *TSNAX-DISC1* noncoding RNA (Sanders et al. 2017); and a recent meta-analysis of young periodontitis patients identified an association in the *FCER1G* gene (De Almeida et al. 2024). Other studies have identified several suggestive loci (Divaris et al. 2013; Teumer et al. 2013; Feng et al. 2014; Hong et al. 2015; Shimizu et al. 2015; Shungin et al. 2019). The phenotypes in previous studies have varied between CDC/AAP diagnosis definitions, increased probing pocket depths (PPD), alveolar bone loss (ABL), clinical attachment loss and self-reported periodontitis. Shared genetic risk loci of aggressive and chronic periodontitis were observed at *SIGLEC5, DEFA1A* and *FCER1G* in a GWAS meta-analysis (Munz et al. 2017). Of these, the association of the *SIGLEC5* locus was verified later (Shungin et al. 2019). Generally, heterogeneity of phenotypes, inadequate sample sizes and overestimation of genetic effects have limited the statistical power in the discovery stage and challenged replication of the results and identification of causal variants contributing to periodontitis (Schaefer 2018). Therefore, new GWA studies with larger sample sizes are needed to identify further genetic variants of periodontitis. Large register-based studies are a valuable source of genetic findings, but their application in dental research has been limited.

The FinnGen study is based on > 500,000 unique samples collected by a nation-wide network of Finnish biobanks (Kurki et al. 2023). The data, representing roughly 10% of the Finnish adult population, are linked by the unique national personal identification numbers to national registers, including those for hospital discharge and primary care. Based on the register data, clinical expert groups have designed > 2000 disease endpoints, including also those representing oral diseases.

To identify genetic risk factors predisposing to periodontitis, we conducted GWAS based on periodontitis diagnosis codes, procedure codes for periodontal treatment and Community Periodontal Indexes (CPI). In addition, we analysed enrichment of functional and regulatory variants, determined protein levels and localisation in gingival tissues and analysed single-cell RNA sequencing data in gingival tissues to further investigate the biological feasibility of our findings. As the highly polymorphic human leukocyte antigen (HLA) genes constitute the strongest genetic susceptibility locus in inflammatory/infectious diseases, we also investigated associations of periodontitis phenotypes with HLA alleles and killer-cell immunoglobulin-like receptor (KIR) gene content.

2 | Methods

Details of the methods used are presented as Supporting Information.

2.1 | Phenotypes and Cohorts

The present FinnGen study (release 11) (Kurki et al. 2023) originally included 473,681 participants with genotype information. We performed analyses among patients who had visited a dentist in the public healthcare sector for a clinical oral examination (NOMESCO codes SAA02-04). All these include full-mouth intraoral and extraoral clinical examinations, including periodontal status. The periodontal examination comprises registration of the presence and location of plaque, periodontal probing depth (PPD) measured from six sites per each tooth, bleeding on probing (BOP), suppuration, furcation defects, plaque retentions, mobility and lost teeth. The codes SAA03-04 include additional examinations. Based on the data registered, we designed three phenotypes: (i) Cases were defined as individuals who had ICD-10 diagnosis code K05.30 (chronic periodontitis), K05.31 (complex periodontitis) or K05.04 (periodontosis), or procedure code for demanding treatment of complex or severe periodontitis (NOMESCO codes SDA12-14) (Figure S1). Controls comprised participants without any diagnosis code for periodontitis or without any procedure codes for demanding periodontal treatment. The other two phenotypes of periodontitis were based on CPI (Ainamo and Ainamo 1985). It was used as (ii) a continuous variable ('CPI-continuous') with the number of sextants with CPI value 4 (PPD ≥ 6 mm) and as (iii) a categorical variable ('CPI-binary') stratified as the presence of CPI 4 (PPD ≥ 6 mm) in at least one sextant versus no CPI 3 or 4 in any sextant (indicating no PPD ≥ 4 mm); that is, controls presented only values 0, 1 or 2.

3 | Results

3.1 | Characteristics

The median ages of diagnosis-based periodontitis patients ($n = 38{,}157$) and controls were 62.8 and 56.3 years, respectively (Table S1). The most frequent ICD10 diagnosis code was K05.30 (chronic periodontitis) followed by K05.31 (complex periodontitis) (Figure S1). CPI data were available for 229,398 subjects with the median age of 48.4 years. The phenotype 'CPI-binary' included 23,674 cases and 149,012 controls with a median age of 63.4 and 44.6 years.

3.2 | GWAS Based on Periodontitis-Diagnosis Identifies Six Independent Loci

Altogether, we identified six genome-wide significant and independent risk loci for periodontitis in four chromosomes: 5, 6, 7 and 8 (Tables 1 and S2, Figure 1A). Locus zoom plots of the significant loci are presented in Figure S2. The most significant locus in chromosome 8 included 11 credible variants and presented the strongest association led by rs7386862. The nearest genes were β-defensins *DEF130A* and *DEF134-6* and pseudogenes *DEF131E*, *DEF131D* and *DEF108E*. The other locus in chromosome 8 with the lead SNP rs1821007 near the *MFHAS1* gene included six significant variants. The significant SNP, rs556937553, in chromosome 7 was a rare variant. The nearest genes of the two loci in chromosome 5 with lead SNPs rs1363972 and rs57650556 were *FST* and *ARL15*. The locus in chromosome 6 near the *PRRT1* gene was led by SNP rs3130277.

TABLE 1 | Lead SNPs in each locus associated with periodontitis phenotypes.

Chr	rsID	Type	Nearest genes	Ref/alt allele	MAF (%)	*p*	*β* (SE)	PP (%)	Other phenotypes[b]
Periodontitis-diagnosis									
5[a]	rs1363972	Intergenic	FST NDUFS4	T/C	24.8	8.97×10^{-9}	0.054 (0.009)	4.6	CPI-bin CPI-con
5	rs57650556	Intron	ARL15	A/G	8.73	2.14×10^{-8}	0.080 (0.014)	5.9	CPI-bin
6	rs3130277	Intergenic	PRRT1 AGPAT1 RNF5 EGFL8	G/C	15.1	4.01×10^{-8}	0.062 (0.011)	—	CPI-bin CPI-con
7	rs556937553	Intron	CPVL CHN2	G/A	0.61	8.08×10^{-9}	0.290 (0.050)	90.6	CPI-bin
8[a]	rs1821007	Intron	MFHAS1 CLDN23	G/A	44.9	3.63×10^{-9}	0.049 (0.008)	26.0	CPI-bin CPI-con
8	rs7386862	intergenic	DEFB130A DEFB134-6 DEFB131E DEFB131D DEFB108E	T/A	25.8	1.68×10^{-9}	−0.070 (0.012)	35.6	CPI-bin CPI-con
CPI-binary									
4	rs1477653215	Regulator	—	G/GCT	0.16	2.28×10^{-8}	0.854 (0.153)	96.4	CPI-con
5[a]	rs72748131	Intergenic	FST NDUFS4	C/T	16.3	3.35×10^{-9}	0.083 (0.023)	9.7	DG CPI-con
6	rs204995	Intron	PBX2 AGER GPSM3 NOTCH4	A/G	15.1	2.63×10^{-8}	0.081 (0.014)	—	DG CPI-con
13	rs41275090	Missense	COL4A1 COL4A2	C/T	0.41	4.77×10^{-8}	0.421 (0.077)	88.1	CPI-con
15	rs549699698	Intron	SNHG14	TCTTTGATTG/T	0.60	4.00×10^{-8}	−0.459 (0.078)	98.8	DG CPI-con
20	rs117935148	Downstream	HMGB1P1 CTCFL	T/A	0.07	4.77×10^{-8}	−1.720 (0.315)	96.2	DG CPI-con
CPI-continuous									
6	rs915894	Missense	NOTCH4 GPSM3 HLA-DQA1	T/G	31.7	2.78×10^{-14}	0.024 (0.003)	—	DG CPI-bin
19	rs429358	Missense	APOE APOC1	T/C	18.2	9.02×10^{-11}	0.025 (0.004)	40.6	—

[a]Low purity according to SuSiE finemapping; Ref, reference; Alt, alternative; MAF, minor allele frequency; PP, posterior probability of being causal.
[b]Significant association with other periodontitis phenotypes; DG, Periodontitis-diagnosis; CPI-bin, CPI-binary; CPI-con, CPI-continuous.

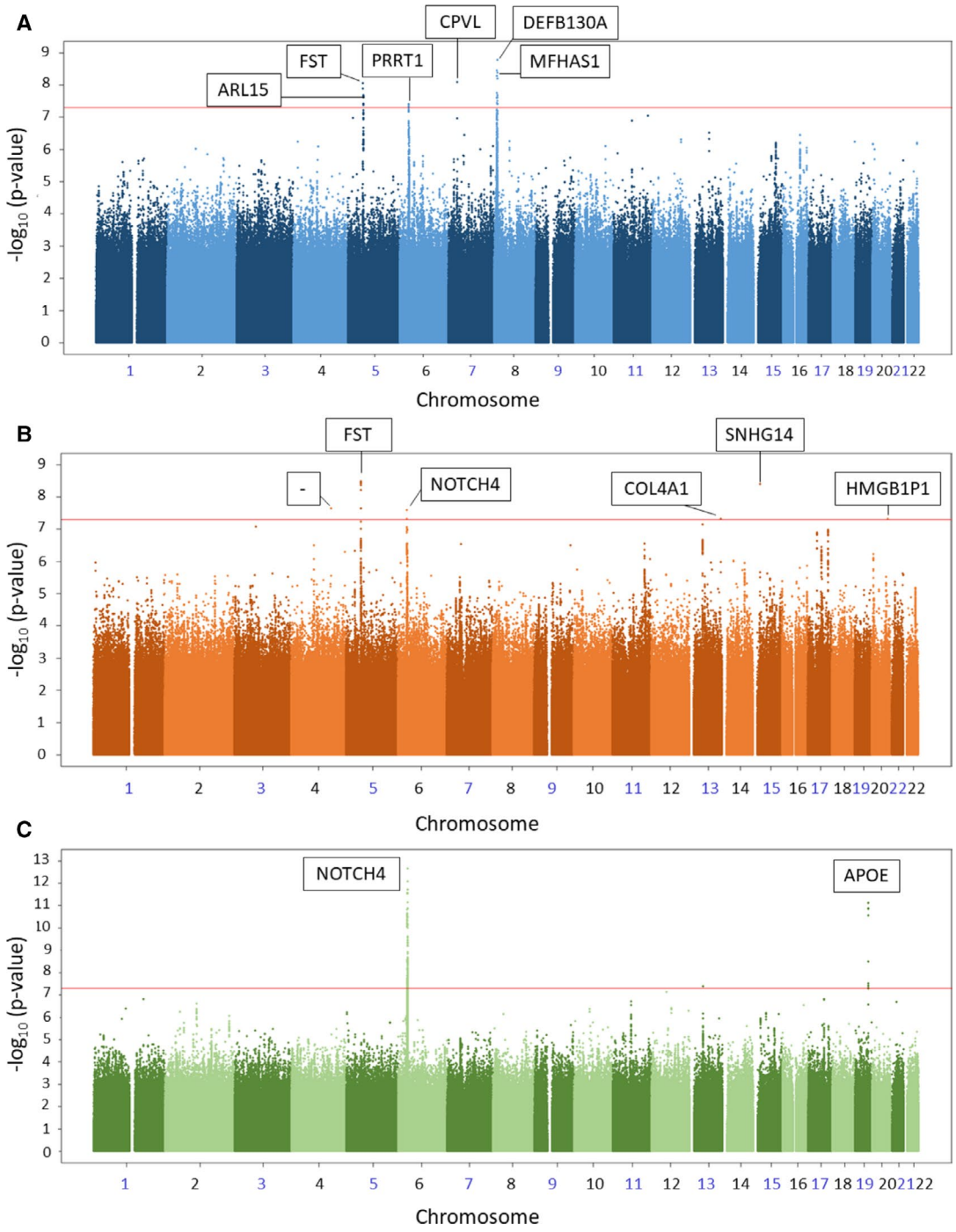

FIGURE 1 | Manhattan plots of genome-wide association study (GWAS) results. We performed three GWASs of periodontitis in the FinnGen population. (A) Phenotype periodontitis-diagnosis, based on ICD-10 diagnosis codes for periodontitis and procedure codes for demanding periodontal treatment. Only participants with a procedure code for clinical oral examination were included in the analysis. (B) Phenotype CPI-binary. Cases had PPD ≥6 mm (CPI 4) in at least one sextant, whereas controls did not have PPD ≥4 mm (CPI 3 or 4) in any sextant. (C) Phenotype CPI-continuous, indicating the number of sextants with PPD ≥6 mm (CPI 4).

Analyses with further adjustments and subgroups are presented in Tables S3–S5.

3.3 | GWAS Based on CPI Identifies Seven Additional Loci

The first CPI-based phenotype, CPI-binary, was associated with genetic variation in six loci (Figures 1B and S3, Table 1). The SNP rs204995 in chromosome 6 is an intron variant near *PBX2, NOTCH4*, *GPSM3* and *AGER* genes. The locus in chromosome 5 with the lead SNP rs72748131 was the same (near *FST*) as above. The other associated loci in chromosomes 4, 13, 15 and 20 included rare variants with minor allele frequencies (MAFs) < 1%. The lead SNPs were a regulatory region variant rs138693228, a missense variant rs41275090 in *COL4A1*, an intron variant rs549699698 in *SNHG14* and a downstream gene variant rs117935148 near *HMGB1P1*. The second phenotype, CPI-continuous, was

associated with two loci in chromosomes 6 and 19 (Figures 1C and S4, Table 1), including the missense variant rs915894 of *NOTCH4* and rs429358 near genes *APOE* and *APOC1*.

As all three periodontal phenotypes displayed associations with variants close to each other in chromosome 6, the locus zooms are presented in Figure 2 for comparison. Altogether, among the 11 independent variants discovered, 5 were rare variants and not investigated further, whereas 6 common variants were novel.

3.4 | Discovery GWAS Results Were Replicated in Other Populations

The lead SNPs located within the HLA region in chromosome 6 (rs3130277, rs915894 and rs204995) were associated with periodontitis in GLIDE (Shungin et al. 2019), whereas the lead SNP of the locus in chromosome 19 near *APOE* was associated with the ABL phenotype in the Parogene cohort (Table S6). Thus, five out of nine (45%) common lead SNPs and three out of six (50%) loci were replicated in external cohorts.

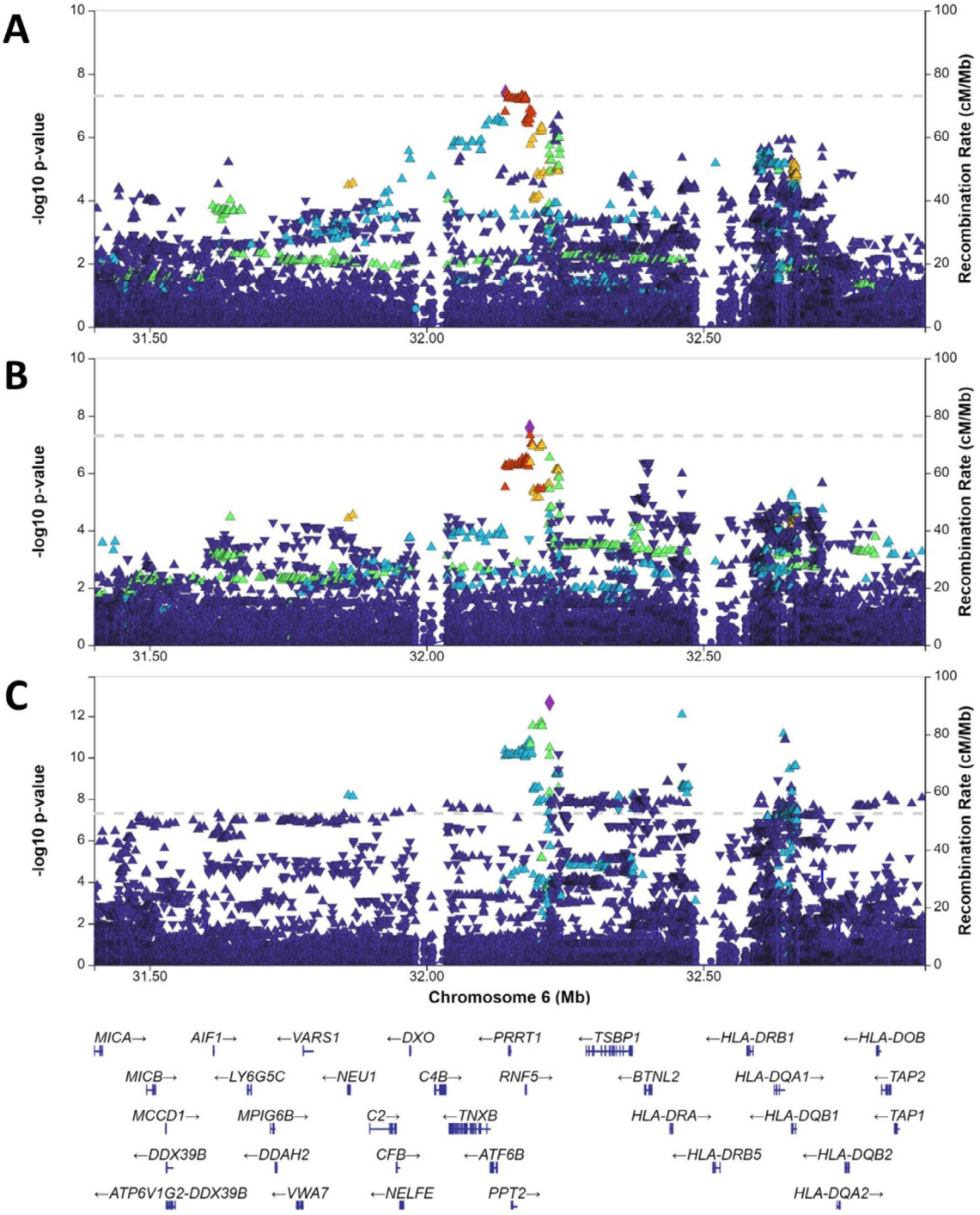

FIGURE 2 | Locus zooms of the genome-wide significant loci in chromosome 6. The GWAS-significant loci in chromosome 6 are shown for all phenotypes; (A) Periodontitis-diagnosis; (B) CPI-binary; (C) CPI-continuous. Locus zooms of other significant findings are presented in Supporting Information.

Among the earlier published 29 GWAS-significant SNPs (Schaefer 2018; Yang et al. 2022), 13 (45%) were not available and 4 (14%) were rare variants (MAF < 1%), whereas 6 (50%) were associated with our phenotypes (Table S7).

3.5 | Periodontitis Phenotypes Are Associated With Common HLA Alleles

We further investigated the HLA alleles in FinnGen (Table 2). The common alleles DRB1*01:01, DRB1*07:01, DQA1*02:01 and DPB1*04:02 were associated with all periodontitis phenotypes. Additionally, DRB1*11:01, DRB3*02:02, DQA1*01:01, DQB1*05:01, HLA-B*35:01 and HLA-C*04:01 were among the protective HLA alleles, whereas DRB3*01:01, DRB4*01:03, DQB1*02:02, DPB1*01:01, HLA-A*01:01, HLA-C*06:02 and HLA-C*07:01 were associated with an increased risk of having periodontitis. As the phenotypes were associated with several HLA class I alleles, which may interact with KIR for further regulation of natural killer (NK) cells, the associations between periodontitis and the KIR gene contents were also analysed (Table S8). However, no significant associations with either inhibiting or activating genes were found.

3.6 | In Silico Analyses

The lead SNP near gene *PRRT* (rs3130277) participates in the regulation of *C4A*, *C4B*, *RNF5*, *NOTCH4*, *FKBPL* and *CYP21A2* genes in multiple tissue types (Table S9). The lead SNP near β-defensin (rs7386862) genes regulates *FAM66A* in several tissues, whereas the lead SNP near the *MFHAS1* gene (rs1821007) down-regulates *ERI1* in fibroblasts and up-regulates *MFHAS1* in regulatory T cells. Rs915894 and rs204995 down-regulate *NOTCH4* in multiple tissues and up-regulate *AGER* in the brain. Cis-eQTLGen identified 27 genes affected by our lead genetic markers. The pQTL platforms recognised 12 proteins associated with rs915894 and rs204995, whereas the lead SNP near *APOE*, rs429358, was associated with the levels of multiple proteins such as apoE, IRF6, MMP-8, IL-10, CRP and apoB. Among the 11 independent loci, 6 lead SNPs were classified into RegulomeDB category 1, and thus likely affect transcription factor binding and gene expression. The most significant protein-coding gene families in GO terms were 'Antigen processing and presentation via MHC class I' and 'via MHC class Ib', 'Classical-complement-pathway C3/C5-convertase complex', 'Chylomicron remnant' and 'Low-density lipoprotein particle' (Table S10).

3.7 | Single-Cell RNA Sequencing (scRNAseq) of Gingival Tissue

To further investigate individual SNPs in gingival tissues, mapping of 30 genes (Table 1) into the two datasets revealed that 21 were enriched in specific cell lineages in both the first study (Williams et al. 2021) and in its validation

TABLE 2 | Significant associations between HLA alleles and periodontitis phenotypes in FinnGen.

			Periodontitis-diagnosis	CPI-binary	CPI-continuous
Gene	**Allele**	**Frequency**	**Beta (SE), FDR**		
DRB1	01:01	0.18	**−0.034 (0.011), 0.047**	**−0.060 (0.014), 0.003**[a]	**−0.020 (0.004), 1.5×10^{-5}**
	07:01	0.06	**0.082 (0.018), 0.0004**[a]	**0.081 (0.023), 0.019**[a]	**0.021 (0.007), 0.019**
	11:01	0.03	0.004 (0.024), 0.99	−0.044 (0.031), 0.61	**−0.027 (0.009), 0.028**
DRB3	01:01	0.18	0.010 (0.011), 0.84	0.029 (0.014), 0.23	**0.014 (0.004), 0.008**
	02:02	0.10	0.001 (0.014), 0.96	−0.011 (0.019), 0.97	**−0.015 (0.005), 0.040**
DRB4	01:03	0.22	**0.034 (0.010), 0.036**	0.034 (0.013), 0.12	0.010 (0.004), 0.055
	01:03 N	0.01	0.088 (0.037), 0.18	0.110 (0.048), 0.18	**0.044 (0.013), 0.013**
DQA1	01:01	0.19	−0.032 (0.011), 0.06	**−0.057 (0.014), 0.003**[a]	**−0.019 (0.004), 2.7×10^{-5}**
	02:01	0.05	**0.082 (0.018), 0.0004**[a]	**0.081 (0.023), 0.019**[a]	**0.021 (0.007), 0.019**
DQB1	02:02	0.04	**0.078 (0.021), 0.018**[a]	0.073 (0.028), 0.11	0.013 (0.008), 0.46
	05:01	0.19	0.031 (0.028), 0.77	**−0.053 (0.013), 0.005**[a]	**−0.018 (0.004), 6.2×10^{-5}**
DPB1	01:01	0.06	0.011 (0.018), 0.90	0.059 (0.022), 0.11	**0.027 (0.006), 0.0005**
	04:02	0.19	**−0.035 (0.011), 0.041**	**−0.047 (0.014), 0.023**[a]	**−0.015 (0.004), 0.002**
A	01:01	0.08	0.032 (0.015), 0.30	0.035 (0.020), 0.38	**0.021 (0.006), 0.003**
B	35:01	0.12	−0.029 (0.013), 0.23	−0.027 (0.017), 0.46	**−0.014 (0.005), 0.035**
C	04:01	0.15	−0.018 (0.012), 0.52	−0.031 (0.016), 0.29	**−0.018 (0.005), 0.0007**
	06:02	0.06	0.052 (0.017), 0.06	**0.072 (0.022), 0.039**[a]	**0.018 (0.006), 0.040**
	07:01	0.12	0.012 (0.012), 0.84	0.025 (0.017), 0.52	**0.015 (0.005), 0.013**

Note: Additive model adjusted for age, sex and genetic principal components 1–10. Significant values are bolded.
Abbreviations: CPI, Community Periodontal Index of Treatment Needs; FDR, false discovery rate; SE, standard error.
[a]Significant also when additionally adjusted for autoimmune diseases.

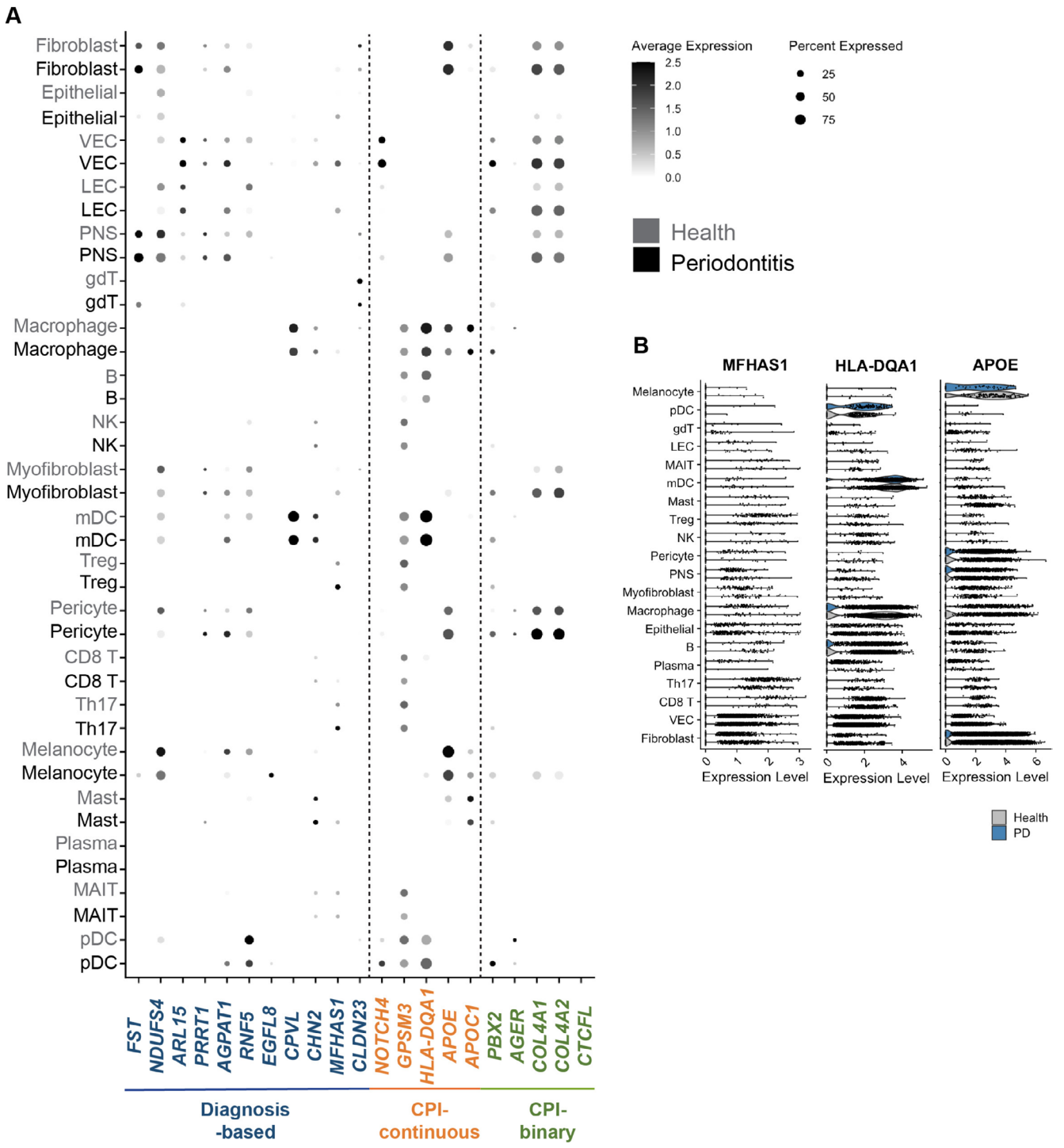

FIGURE 3 | Expression of the identified risk genes across human gingival cell subsets. (A) Dot plot showing the normalised and scaled average expression of identified genes (Table 1) and percentage of expressing cells across phenotypes, and in both health and periodontitis. gdT, gamma delta T cells; LEC, lymphatic endothelial cells; MAIT, mucosal-associated invariant T cell; mDC, conventional dendritic cell; NK, natural killer; pDC, plasmocytoid dendritic cell; PNS, peripheral nervous system; Treg, regulatory T cell; VEC, vascular endothelial cells. (B) Violin plot highlighting expression of *MFHAS1, HLA-DQA1* and *APOE*.

(Caetano et al. 2021) (Figures 3, S5 and S6, Table S11). They included *NOTCH4* in vascular endothelial cells, *HLA-DQA1* in macrophages and dendritic cells and *COL4A1* and *COLA2* in endothelial cells and fibroblasts. *MFHAS1* was enriched in epithelial cells, fibroblasts, T cells and endothelial cells, whereas *FST* was enriched in fibroblasts and peripheral nervous system (PNS) cells.

3.8 | *MFHAS1* in Periodontium

As our GWAS revealed an association between periodontitis and variation near the *MFHAS1* gene, which was not described earlier in relation to periodontitis, we visualised this protein in the gingival tissue of both periodontitis patients and healthy subjects (Figure 4). Immunohistochemical analyses of gingival

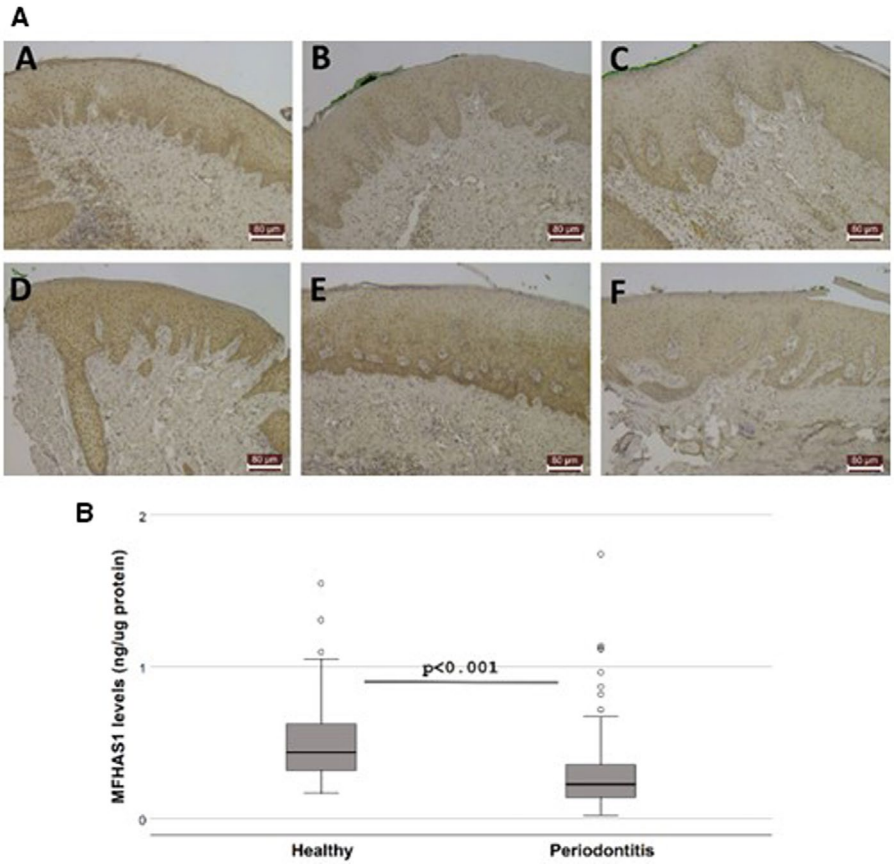

FIGURE 4 | MFHAS expression studied in gingival granulation tissues. (A) Gingival expression and localisation of MFHAS1 in periodontally healthy (A–C) and in periodontitis (D–F) tissues. MFHAS1-positive cells were observed as yellow to brown colour, depending on the staining intensity. (B) Altogether 80 granulation tissue samples from 43 stage III/IV grade C periodontitis patients and 41 samples from 41 periodontally healthy controls were included. Tissue samples were ground, homogenised and ultrasonicated. Tissue MFHAS1 levels were measured using commercial ELISA kits and the levels were normalised for the protein concentrations. *p*-value is given over the connector line.

tissues revealed that MFHAS1 was detectable in both the epithelium and connective tissue, being stronger in the former. MFHAS1 staining was detectable in all epithelial layers, especially at the stratum basale, whereas in the connective tissue the stained cells were more randomly distributed. Using ELISA, MFHAS1 was detected in all gingival tissue samples, and the levels were higher in healthy individuals ($p < 0.001$) than in periodontitis patients.

3.9 | Associations With Other Phenotypes in FinnGen

The top SNPs identified in our GWAS were associated with multiple other phenotypes in FinnGen (Table S12). Obviously, the variation in the HLA region was strongly associated with autoimmune diseases. The lead SNPs rs1821007, rs145494467 and rs138322411 were associated with cardiometabolic phenotypes such as hypertension, obesity, type 2 diabetes, cardiovascular diseases and peripheral vascular diseases. Rs429358 near *APOE* was strongly associated with several dementia phenotypes, dyslipidemia, coronary atherosclerosis and bacterial diseases.

Heritability (h^2) of periodontitis was 0.13 and 0.08 for the periodontitis-diagnosis and CPI-binary phenotypes, respectively. Among other traits, periodontitis phenotypes had the strongest genetic correlation (r_g) with smoking status, followed by 'other septicaemia' and 'other bacterial diseases' (Figure 5, Table S13). Also, several cardiovascular and cardiometabolic phenotypes and their comorbidities, such as stroke, coronary heart disease, obesity, type 2 diabetes, hypertension and dyslipidemia, showed strong genetic correlation with periodontitis. Finally, other oral disease phenotypes such as pulpitis, endodontic infections and caries showed significant genetic correlations with periodontitis phenotypes (r_g 0.21–0.38). The genetic correlation between the periodontitis phenotypes varied between 0.73 and 0.99 (Table S14).

4 | Discussion

We identified 11 novel loci that are associated with periodontitis in our GWAS uing the national register data on periodontal health and disease. Five variants were rare and not studied further. Half of the six common variants could be replicated in external cohorts. The discovery analysis comprising approximately 250,000 Finnish individuals represents the largest GWAS of periodontitis so far and revealed several novel loci associating with periodontitis. In our translational analyses linking genetics to functionality, several lead SNPs participated in the regulation of multiple genes in various tissues, such as plasma, immune cells and—importantly—gingival

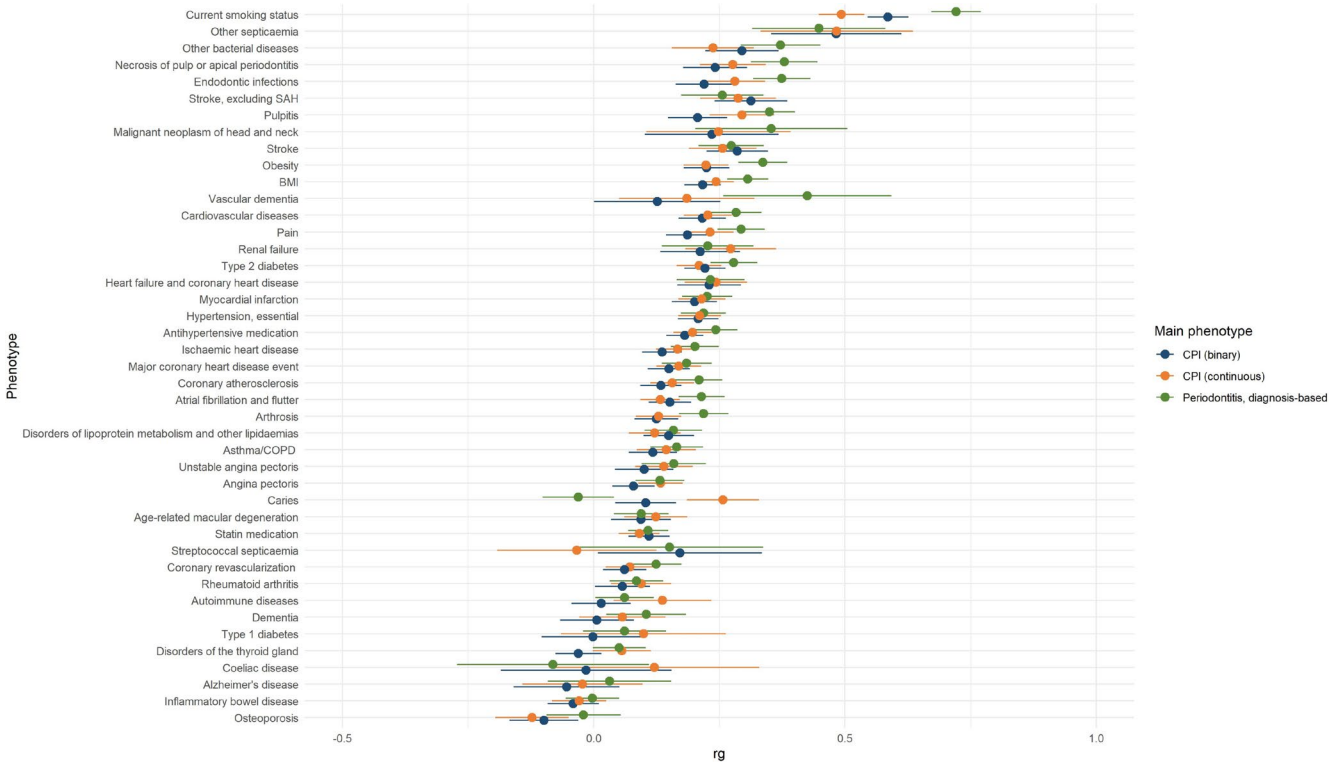

FIGURE 5 | Genetic correlations between periodontitis and other clinical phenotypes. Genetic correlations were investigated using linkage disequilibrium score regression. Pairwise genetic correlations (r_g) between the phenotypes quantifying the shared genetic variance relative to the square root of their respective SNP heritability estimates are presented.

tissues. Our GWAS disclosed the importance of genetic variations in the HLA region in the risk of all studied phenotypes. Further analyses using imputed HLA alleles indicated that especially HLA-DRB1, HLA-DPB1 and HLA-DQA1 might be involved in periodontitis independently of autoimmune diseases. Phenotypical and genetic correlations associated periodontitis with several bacterial diseases, autoimmune diseases, cardiometabolic phenotypes as well as other oral/dental diseases. Overall, this GWAS provides a clear picture of the importance of both adaptive and innate immune system arms in the pathogenesis of periodontitis as well as the systems linking them, that is, complement and HLA.

All phenotypes of the present study were associated with genetic variation in the HLA region on chromosome 6 (Lokki and Paakkanen 2019). Periodontitis has previously been associated with genetic variation in the BAT1-NFKBIL1-LTA region within HLA Class III (Kallio et al. 2014). In the present study, the associated region within Class III included genes such as *PRRT1*, *AGER*, *PBX2*, *NOTCH4*, *AGPAT1*, *RNF5* and *PPT2*. *AGER* overlapping with *PBX2* belongs to the immunoglobulin superfamily. Its polymorphism has been associated with an unfavourable proinflammatory state implicated in multiple inflammatory, autoimmune and cardiovascular diseases (Serveaux-Dancer et al. 2019). In the present study, the variation near *NOTCH4* was associated with its down-regulation in several tissues, suggesting decreased Notch signalling, which may affect alveolar bone homeostasis (Jakovljevic et al. 2023). The lead SNP within *PPT2* was associated with the up-regulation of C4B and down-regulation of C4A in multiple tissues, linking complement activation pathways with periodontitis risk. Complement component C4 has an essential role in the functioning of classical and lectin pathways for recognition and elimination of invading microbes (Wang and Liu 2021). Thus, our results are in line with earlier evidence indicating that the activation of complement is central to the pathogenesis of periodontitis (Hajishengallis 2015). The phenotypes composed of CPI were associated with HLA Class I alleles, which are expressed in all nucleated cells and present foreign peptides to killer T cells (Lokki and Paakkanen 2019). Specific HLA Class I molecules and KIR interact for the recognition and destruction of unhealthy cells, thus increasing the ability of the immune system to distinguish self from non-self (Ritari et al. 2022). KIR gene contents, however, did not associate with periodontitis phenotypes.

The locus within HLA class II included significant SNPs within genes such as *HLA-DRB1*, *HLA-DQA1* and *HLA-DQB1*. Furthermore, HLA types generated using a population-specific HLA reference panel (Ritari et al. 2020) supported these results, because especially the alleles DRB1*07:01, DQA1*02:01 and DQB1*02:02 were associated with the risk of periodontitis, whereas the alleles DRB1*01:01 and DPB1*04:02 showed protective associations. Class II HLA molecules are expressed in professional antigen-presenting cells, forming the base for the humoral immune response activated by microbial exposures (Lokki and Paakkanen 2019). Indeed, periodontitis is driven by a dysbiotic microbiome, which triggers antibodies binding to both bacteria and also the host epitopes (Pietiäinen et al. 2018). Therefore, the autoimmunological characteristics of periodontitis (Suárez et al. 2020) may derive from genetic predisposition associated with variation in the HLA region.

Our findings support the hypothesis that shared genetic susceptibility may be one of the mechanisms linking Alzheimer's disease and periodontitis (Ryder and Xenoudi 2021). The number of sextants with PPD ≥ 6 mm was associated with four variants within the *APOE* gene led by rs429358 encoding the ε4 allele, the landmark of Alzheimer's disease risk (Saunders et al. 1993). ApoE4 with its poor binding to complement factor H (CFH) induces neuroinflammation (Chernyaeva et al. 2023). Polymorphisms of CFH and apoE have been earlier associated with periodontal parameters and aggressive periodontitis (Salminen et al. 2022; Gao et al. 2015). Another disease group linked to periodontitis is atherosclerotic cardiovascular diseases (Lockhart et al. 2012). ApoE plays a crucial role on multiple levels in atherogenesis not only by increasing the number of pro-atherogenic lipoproteins regulating LDL and VLDL metabolism but also by participating in the immunoregulation (Mahley et al. 2009). Overall, the genetic components of periodontitis were significantly correlated with stroke, coronary heart disease, obesity, hypertension and type 2 diabetes. Interestingly, periodontitis had a genetic correlation with 'Other septicaemia', but not with 'Streptococcal septicaemia'. Periodontal patients experience bacteraemia and endotoxaemia (Pussinen et al. 2022), which may lead to sepsis in susceptible individuals.

Expression of the identified risk genes across human gingival cell subsets highlighted key cell types in periodontitis, increasing the credibility of the GWAS findings. Some cell subsets were particularly enriched for the expression of genes near our lead SNPs across all three phenotypes. Such cell types were endothelial cells, antigen-presenting cells (macrophages and dendritic cells) and fibroblasts—lineages that are important in the pathogenesis of periodontitis. In addition to known associations—such as *NOTCH4* in vascular endothelial cells, *HLA-DQA1* in macrophages and dendritic cells and *COL4A1* and *COLA2* in endothelial cells and fibroblasts (Caetano et al. 2021)—we also identified new associations, such as *MFHAS1* in epithelial cells, fibroblasts, T cells and endothelial cells. Our immunohistochemical analyses of gingival tissue samples localised MFHAS1 in connective tissue and all epithelial layers, but especially at the stratum basale. MFHAS1 functions as a TLR4 suppressor, which essentially reduces inflammatory response (Shi et al. 2017). Based on our findings, MFHAS1 levels are decreased in gingival tissues of periodontitis patients, supporting the anti-inflammatory role of this protein.

A major strength of our study is the large sample size of almost 250,000 participants with diverse registery data. The integration of genetic information from so many individuals with their national health registry data is unique and facilitates the discovery of novel risk and protective variants for periodontal diseases. Our three periodontal phenotypes represent different disease characteristics: Periodontitis-diagnosis includes patients receiving diagnosis at any stage of severity. Two other phenotypes were based on CPI value 4 as a proxy for periodontitis diagnosis. Using the phenotype CPI-binary enabled us to compare the extremes with at least one PPD ≥ 6 mm versus those without any deepened periodontal pockets, whereas the phenotype CPI-continuous considered whether PPD ≥ 6 mm was localised or generalised. The phenotypes displayed both overlapping and different genetic risk profiles: Periodontitis-diagnosis and CPI-binary resembled each other, associating with antigen processing and presentation and regulation of memory T cells. The phenotype CPI-continuous linked periodontitis strongly to systemic consequences through lipoprotein metabolism, which plays an essential role in modulating inflammation (Khovidhunkit et al. 2004).

Some limitations must be acknowledged. Originally, the Finnish nationwide electronic health registers were established for administrative purposes to monitor the use of healthcare services of Finnish residents. Even though they are nationally and widely utilised, their main limitation may derive from diagnostic challenges. The recording has been done by numerous dentists, and false negatives may be present, because periodontitis often remains undiagnosed. Although periodontal examinations are based on full-mouth periodontal probing, the registered information is limited to dichotomous diagnosis codes or CPI index at the sextant level. However, the prevalence of the diagnosis was 15.4% among all participants, thus being close to the frequency of subjects having deepened periodontal pockets in ≥ 8 teeth according to a Finnish population-based survey (24%) (Suominen et al. 2018). Among the 10 different loci associated with two binary phenotypes, 5 variants were rare with MAF below 1%. Despite the statistical power provided by the large population and the known Finnish population isolates (Kurki et al. 2023), these findings should be interpreted with caution. Although FinnGen can be used to find low-frequency variants with high impact, the findings should be confirmed using additional statistical methods, and were thus not considered further in the present study. Our sample size was sufficiently large for the linkage disequilibrium (LD) score regression analysis, and the heritability of periodontitis was on the same range (8%–13%) as in earlier GWA studies on periodontitis (Nibali et al. 2019). The fact that data derived from GWA analyses do not capture all genetic variation may lead to an underestimation of the true heritability. This is obvious compared to twin studies, where the heritability of periodontitis is typically higher, reaching up to 40% (Nibali et al. 2019). Additionally, comorbidities, across especially older age groups, could have affected the results. All results were adjusted for age, but the subgroup analyses including participants < 50 years representing 35%–50% of the population presented attenuated *p*-values, suggesting that the comorbidities having genetic correlations with periodontitis may have affected the results. The genetic correlation was especially notable with current smoking status (r_g 0.5), which had a stronger impact on the *p*-values in the adjusted model than diabetes (r_g 0.2). Thus, smoking may be a mediator of vertical pleiotropy in the analyses. Horizontal pleiotropy was observed between several examined phenotypes which were associated with the same genetic variation: for example that observed in the HLA region. Although we identified plausible associations between immune system arms and periodontitis, caution is warranted in interpreting the aetiological implications of these findings. Given the complexity of pleiotropic effects and gene–environment interactions in our sample, future studies that adjust for these effects will help distinguish disease-specific risk variants from those driven by pleiotropy.

The present genome-wide study demonstrates that genetic variation contributing to immune dysregulation and lipoprotein metabolism is involved in the pathogenesis of periodontitis, which has considerable genetic similarity with other complex traits.

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Ethics Statement

All studies were done in accordance with the Declaration of Helsinki. Based on the Finnish biobank act, participants entered the FinnGen study by signing an informed consent for biobank research (Kurki et al. 2023). The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the FinnGen study protocol Nr HUS/990/2017. An informed consent was obtained from participants in the Parogene cohort, and the Ethics Committee of the Helsinki University Hospital, Finland, approved the study plan.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Finnish biobank data can be accessed through the Fingenious services (https://site.fingenious.fi/en/) managed by FINBB (https://finbb.fi/). Finnish Health register data can be applied from Findata (https://findata.fi/en/data/). Summary statistics are available at: https://storage.googleapis.com/fg-publication-green-public/F_2023_026_20250625/summary_statistics_periodontitis.zip.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.