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Host genetics role in the pathogenesis of periodontal disease and caries

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Abstract

Background: This study aimed to produce the latest summary of the evidence for association of host genetic variants contributing to both periodontal diseases and caries.

Materials and Methods: Two systematic searches of the literature were conducted in Ovid Medline, Embase, LILACS and Cochrane Library for large candidate gene studies (CGS), systematic reviews and genome-wide association studies reporting data on host genetic variants and presence of periodontal disease and caries.

Results: A total of 124 studies were included in the review (59 for the periodontitis outcome and 65 for the caries outcome), from an initial search of 15,487 titles. Gene variants associated with periodontitis were categorized based on strength of evidence and then compared with gene variants associated with caries. Several gene variants showed moderate to strong evidence of association with periodontitis, although none of them had also been associated with the caries trait.

Conclusions: Despite some potential aetiopathogenic similarities between periodontitis and caries, no genetic variants to date have clearly been associated with both diseases. Further studies or comparisons across studies with large sample size and clear phenotype definition could shed light into possible shared genetic risk factors for caries and periodontitis.

Key words: caries; genetic; periodontitis

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Inflammatory periodontal diseases and caries are the most common bacteria-mediated diseases of mankind despite being highly preventable. Periodontal diseases are characterized by an inflammatory reaction against members of the oral microbiota (Curtis 2015) and, among them, Periodontitis (PD) leads to apical migration of the epithelial attachment and resorption of connective tissue and alveolar bone, often resulting in early tooth loss. Heritability has long been thought to play an important role in the predisposition to periodontitis (Baer 1971). Genetic factors are now thought to determine about half the variance of periodontitis risk in the population (Michalowicz et al. 1991). Common single-nucleotide polymorphisms (SNPs) able to affect gene activity or protein production, with an effect on structural factors of the periodontium or on the host response to microbial challenge, are among possible risk factors for periodontitis. However, despite research dating back nearly two decades (Kornman et al. 1997), no single gene variant has yet clearly emerged as definitely predisposing to periodontitis.

Caries leads to continued localized mineral loss from the dental enamel and as it progresses, subclinical mineral losses become visible (white spot lesions) and eventually unsupported enamel collapses (cavities) (Vieira 2016). Caries is traditionally described as the interplay among a susceptible host, microbiota and diet (Keyes 1960). The factors defining the susceptible host are under genetic control and the

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evidence for a genetic component to caries can be sourced from studies of family patterns in twins (Boraas et al. 1988, Conry et al. 1993), families (Klein & Palmer 1940) and animal breeding (Hunt et al. 1944). Depending on the surrogate measure of the disease employed, genetics explain 25–64% of the variance of the disease seen in the population (reviewed in Vieira et al. 2014).

Since both periodontitis and caries are bacteria-mediated oral diseases and depend on how the host responds to the presence of infectious agents, it is reasonable to hypothesize that some of the same genes may have pleiotropy in both diseases, particularly in regards to immune responses, but possibly also related to dental structure formation, quality of saliva and behaviours dictating compliance with oral hygiene practices.

Studies to identify SNPs and other genetic variants predisposing to periodontitis and to caries consist mainly of hypothesis-testing candidate gene/loci and hypothesis-generating genome-wide association studies (GWAS). This review aimed to systematically appraise the existing literature (both hypothesis-testing and hypothesis-generating) on gene variants associated with periodontitis and caries to identify possible common genetic pathways leading to both diseases.

Material and Methods

A systematic review protocol was written in the planning stages and the PRISMA checklist (Moher et al. 2009) was followed both in planning and reporting this review (checklist attached as Appendix S1). Since the body of work in the two fields (periodontology and cariology) in regards to mapping genes for the two diseases is very distinct, this report was written as follows. A robust systematic review of the entire gene mapping effort of the periodontal field was performed, taking into account hypothesis-testing and hypothesis-generating studies. The results of this review were then cross-referenced with the significantly more limited literature of mapping genes for caries. A systematic review for caries was published recently by one of the authors (Vieira et al. 2014) and the original search was complemented to add more recent publications.

Focused question

- The question addressed was the following: What is the association between host genetic factors and presence of periodontal disease? Are any of these host genetic factors associated with both caries and periodontal disease?

PECO (Population Exposure Comparison Outcomes) outline for periodontal disease review

- Population: subjects affected with inflammatory plaque-induced periodontal disease.
- Exposure: analysis of host genetic factors (gene variants).
- Comparisons: control subjects with no inflammatory plaque-induced periodontal disease.
- Outcomes: presence of inflammatory plaque-induced periodontal disease.

Eligibility criteria (periodontal disease)

Human studies reporting data on host genetic variants associated with inflammatory plaque-induced periodontal disease (including chronic periodontitis (CP), aggressive periodontitis and gingivitis) were considered suitable for this review. Inclusion criteria were as follows:

- Study designs:
  - Systematic reviews of candidate gene studies (CGS).
  - Candidate gene studies (including at least 1000 cases and controls and not included in the systematic reviews above).
  - Genome-wide association studies.
- Reporting measures of periodontal disease (periodontal diagnosis).
- Reporting analysis of host genetic variants (SNPs).

Eligibility criteria (caries)

Human studies reporting data on host genetic variants associated with caries were considered suitable for this review. Inclusion criteria were as follows:

- Study designs:
  - Candidate gene studies.
  - Systematic reviews of CGS.
  - Genome-wide linkage or association studies.
- Reporting measures of caries (caries experience and determination of affected status to be used in the genetic analyses).
- Reporting analysis of host genetic variants (SNPs, microsatellite markers, biochemical markers).

Exclusion criteria were:

- Case reports.
- Studies on animal models.

Information sources

The literature search to identify eligible systematic reviews and GWAS was conducted in Ovid Medline, Embase, Cochrane Library and LILACS (up to 20 March 2016). A second search to identify eligible large periodontal CGS was conducted in Ovid Medline and Embase (from 1994 up to 30 May 2016). The reference lists of included articles and relevant reviews were manually searched. The search was complemented by a hand search of the journals most likely to publish studies on this topic in the last 20 years (*Journal of Clinical Periodontology, Journal of Dental Research, Journal of Periodontal Research* and *Journal of Periodontology, Caries Research, BMC Oral Health, PLoS ONE*).

Search strategy

The search strategy used is described in Appendix S2.

Study selection

In the case of periodontal disease, studies were selected in two-stage screening and carried out by two independent reviewers (authors A.D.I. and L.N.). Disagreements about inclusion or exclusion of a study were resolved by discussion. Author A.R.V. screened studies for the "caries" outcome. The first-stage screening of titles and abstracts

eliminated articles that did not meet the inclusion criteria. At the second-stage full-text screening, the study eligibility was verified independently by the reviewers and the data extraction and quality assessment were performed for the included studies. The level of agreement between reviewers was calculated using Kappa statistics for first and second-stage screening.

Data collection process/data items

Data were extracted based on the general study characteristics, including setting, year, number of subjects included, study methods and results.

Risk of bias in individual studies

The risk of bias of the included periodontal studies was assessed through sensitivity analysis using:

- The AMSTAR checklist for systematic reviews (a total of 12 items including the addition of a point on "disease definition") (see Appendix S3).
- The risk of bias of the included GWAS and CGS was assessed through sensitivity analysis using a recently proposed score of 0–20 adapted to genetic analyses of periodontal studies (Nibali 2013).

Summary measures/synthesis of results/statistical methods

No meta-analysis was attempted for this systematic review, hence no formal statistical analyses were performed.

Summary of strength of evidence

Specific criteria were set to summarize the strength of evidence for associations of genes and SNPs with periodontal disease based on reviewed CGS, systematic reviews and GWAS (see Appendix S4). According to these criteria, the evidence was considered "strong," "moderate," "weak" or "very weak." Genes associated with periodontal disease established by these criteria were cross-referenced with the caries search to identify possible common genes associated with both diseases.

Results

Study selection

Figure 1 reports the flowchart representing study selection and inclusion for the periodontal disease and caries systematic review. A total 59 papers were finally included for the "periodontitis" outcome. The kappa value for inter-reviewer agreement was 0.94 at title and abstract screening and 1.0 at full-text reading. For the "caries" outcome, 65 papers were included for analysis (see Fig. 1). No

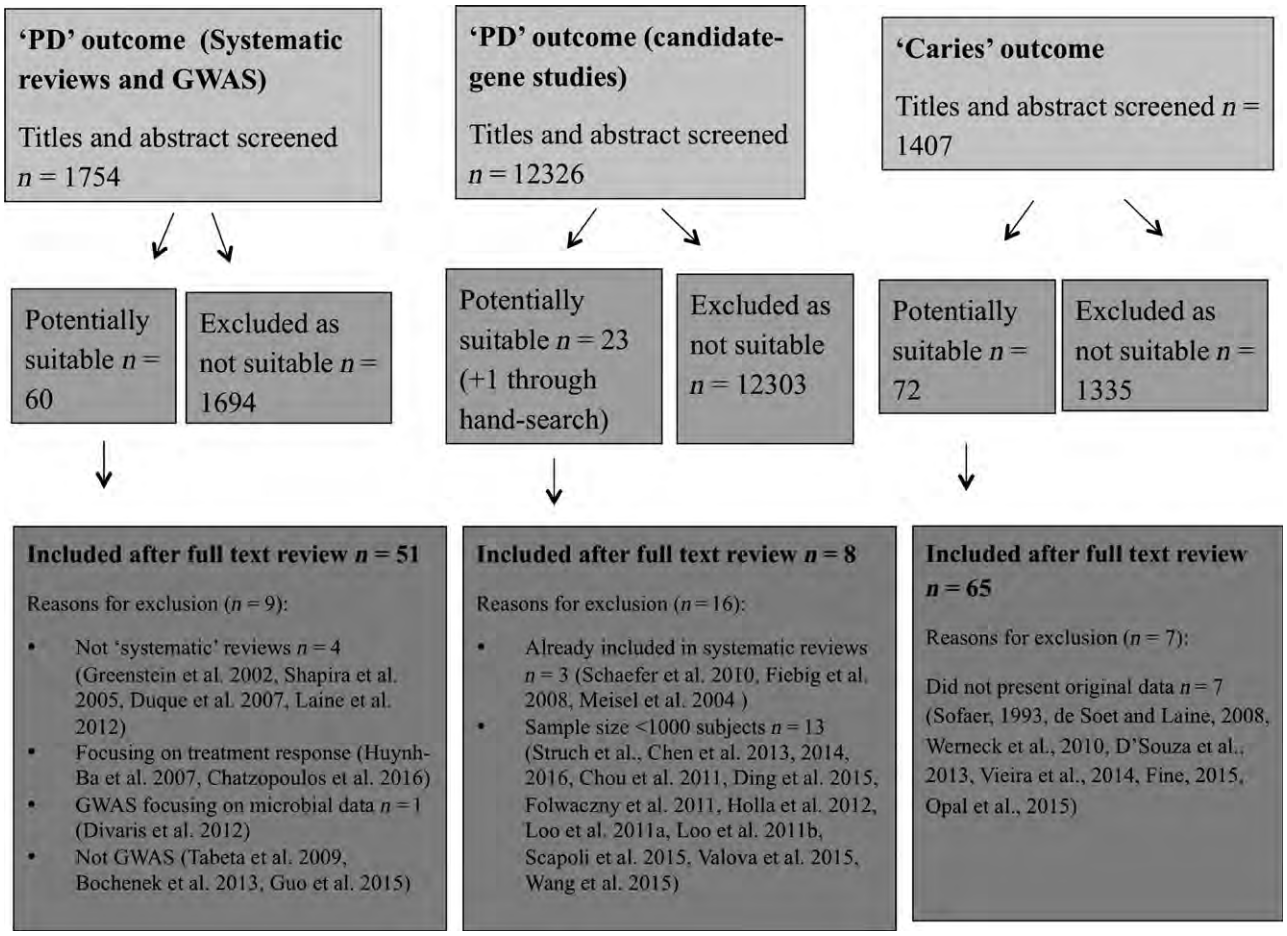

Fig. 1. Flowchart of study inclusion. PD, periodontitis; GWAS, genome-wide association study.

systematic reviews on the subject were detected.

Study characteristics

Tables 1–3 report the characteristics of the 59 reviewed studies for the "periodontal disease" outcome (respectively, systematic reviews, CGS and GWAS). The reviewed papers had been published in the last 9 years, from 2008 to 2016. Table 4 describes the characteristics of the 65 reviewed studies for the "caries" outcome (respectively, candidate gene and genome-wide linkage and association studies). The reviewed papers were published between 1981 (biochemical markers for the HLA locus) and 2016.

Synthesis of results

- Periodontal disease:
  - Systematic reviews focused on a wide range of SNPs (Table 1), mainly affecting inflammatory and immune responses. Several reviews assessed the same SNPs, the most common being in the Interleukin-1 (IL1) gene. A range of 3–53 papers were included in the various systematic reviews. Owing to the clearly skewed distribution of genotypes across different ethnicities, results relative to subjects of different ethnic groups were ignored in the present review and only results restricted to specific ethnic groups are presented (generally "Caucasians" and "Asians" subgroup analyses were reported). Furthermore, only results relative to allelic distribution and dominant or recessive genotype models are reported (e.g. CC *versus* CT + TT genotypes but no additive model CC *versus* TT). Meta-analysis results with high heterogeneity based on I^2 test > 50% (Higgins et al. 2003) or $p < 0.10$ were not considered consistent and are not reported in the table. Some papers focused on just one SNP, while others focused on several SNPs. Systematic reviews generally included case–control or cross-sectional studies on patients with periodontitis *versus* controls and reporting data on genotype and allele distribution. Some reviews excluded studies based on patients' medical history or studies not in Hardy–Weinberg equilibrium (HWE). Some studies focused only on CP, others on Aggressive Periodontitis (AgP) and some on both, whereas no studies specific to gingivitis outcomes were detected. The majority of studies reported some statistically significant associations between presence of periodontitis and analysed SNPs, with some exceptions. The effect sizes of associations between SNPs and the periodontitis trait are reported for cases showing statistical significance.
  - Candidate gene studies included a range of 89–600 periodontitis patients and 64–1448 controls in the "discovery sample." Several of these studies also had a replication sample, while other lacked it. "Periodontitis" and "health" definitions varied according to the different studies. Genetic methods and candidate gene and SNPs varied in the different studies and are reported in Table 2.
  - Genome-wide association studies included a range of 99–2681 periodontitis patients and 529–1823 controls. "Periodontitis" and "health" definitions varied according to the different studies. Most GWAS included replication samples. Genetic methods, SNPs exclusions and statistical significance thresholds varied in the different studies (see Table 3 for details).
- Caries:
  - Candidate gene studies have focused on genes involved in enamel formation, in the immune system, and saliva for the most part. Studies range from 50 subjects to a few thousand. Besides sample sizes and presumed limited statistical power, studies also vary in the phenotype definition, covariates analysed and gene markers studied (Table 4).
  - Genome-wide searches for caries have been done by linkage (Vieira et al. 2008) and association (GWAS, Shaffer et al. 2011, Wang et al. 2012a, Morrison et al. 2016). Sample sizes also varied from a few hundred to 12,000. A major limitation is the way the phenotype is defined, particularly in the GWAS, and these studies suffer from lack of statistical power, lack of covariate data and heterogeneity (Table 4).

Publication bias analysis

Appendices S5 and S6 report results of risk of bias analysis of individual studies included in the present review. Periodontitis systematic reviews (Appendix S5) ranged in modified AMSTAR score from 3 to 8. Candidate gene study (CGS) and GWAS in periodontitis (Appendix S6) ranged in risk of bias scores (Nibali 2013) from 12 to 17. Quality assessment was not performed for the "caries" outcome, as this search was mainly used for explorative purposes to cross-check with the "periodontal disease" outcome. However, the heterogeneity of phenotype definition based on caries experience was noticed.

Strength of evidence for association with periodontal disease

Table 5 reports summary of genes associated with the "periodontitis" outcome as determined from data extraction of papers included in the present review. Based on the "strength of evidence" criteria selected a priori (Appendix S4), three genes emerged as having strong level of evidence with periodontitis:

- Vitamin D Receptor (*VDR*) gene: SNPs in the *VDR* gene were associated with periodontitis in several CGS; the association with CP was confirmed in a meta-analysis in Asians for TaqI t allele and with AgP for the FokI f allele (Chen et al. 2012), although an earlier meta-analysis had not found significant associations with low heterogeneity (Deng

Table 1. Summary of characteristics and main results of systematic reviews on candidate gene studies with outcome presence of "periodontal disease"

Authors and country	Separate analyses by ethnicity	No. studies included	Total number of cases	Total number of controls	Comparisons	Exclusions*	SNPs analysed	Significant associations
Chen et al. (2015) (China)	Caucasian, Asian	25	1594	2483	AgP, healthy	AgP patients with systemic diseases	*IL1B* +3954 (rs1143634)	None
Hu et al. (2015) (China)	Caucasian, Asian	20	965	1234	AgP, healthy	nr	*IL1B* −511 (rs16944) and +3954 (rs1143634)	None
Wang et al. (2014) (China)	Caucasian, Asian, "Negroid"	19	1266	2134	AgP, healthy	Unclear diagnosis of AgP, systemic diseases	*IL1A* −889 (rs1800587) and +4845 (rs17561)	None
Deng et al. (2013) (China)	Caucasian, Asian	36	3095	2839	CP, healthy	nr	*IL-1B* +3954 (rs1143634)	CP in Caucasians: T *versus* C allele (OR: 1.21, CI: 1.07–1.37), TT *versus* TC + CC (OR: 1.71, CI: 1.33–2.20), CC *versus* CT + TT (OR: 1.19, CI: 1.02–1.38) (after elimination of studies causing heterogeneity)
Karimbux et al. (2012) (USA-UK)	Caucasian	13	1244	710	CP, healthy	Systemic diseases, age < 35	*IL1A* −889 (rs1800587) and +4845 (rs17561), *IL1B* +3954 (rs1143634), *IL1* composite genotype	CP in Caucasians: IL1A −889 and +4954 (OR: 1.48, CI: 1.17–1.86)
Ma et al. (2015) (China)	Chinese, Indian	20	1656	1498	CP, healthy	Systemic diseases	*IL1B* +3954 (rs1143634)	CP in Asians: TT + CT *versus* CC (OR: 1.60, CI: 1.02–2.52, $p = 0.04$); T *versus* C (OR: 1.60, CI: 1.06–2.42, $p = 0.02$)
Mao et al. (2013) (China)	Caucasian, Asian, Brazilian	23	2122	1794	CP, healthy	Systemic diseases	*IL1A* −889 (rs1800587) (+4845 rs17561)	CP in Caucasians: T *versus* C allele (OR: 1.31, CI: 1.15–1.49), TT + CT *versus* CC (OR: 1.33, CI: 1.13–1.58) CP in Asians: TT *versus* CT + CC (OR: 2.85, CI: 1.84–4.42)
Yin et al. (2016) (China)	nr	6	336	366	"Periodontitis" (not specified), healthy	nr	*IL1A* +4845 (rs17561) and *IL1B* +3954 (rs1143634)	Not specified by ethnicity

Table 1. (continued)

Authors and country	Separate analyses by ethnicity	No. studies included	Total number of cases	Total number of controls	Comparisons	Exclusions*	SNPs analysed	Significant associations
Nikolopoulos et al. (2008) (Greece)	Caucasian, Asian	53	4178	4590	CP, AgP, healthy	nr	*IL1A* −889 (rs1800587) and +4845 (rs17561), *IL1B* +3954 (rs1143634) and −511 (rs16944), *IL1* composite genotype, *IL6* −174 (rs1800795), *TNF*-α 308G/A (rs1800629)	CP in Caucasians: IL1A −889 T *versus* C allele (OR: 1.31, CI: 1.03–1.67), CC *versus* CT + TT (OR: 1.66, CI: 1.27–2.18) CP in Asians: IL 1B +3954 CC *versus* CT + TT (OR: 2.42, CI: 1.49–3.94); IL1B −511 C *versus* T allele (OR: 1.99, CI: 1.22–3.23), CC *versus* CT + TT (OR: 1.89, CI: 1.12–3.18)
Shao et al. (2009) (China)	Caucasian, Asian, Brazilian	6	1093	574	CP, AgP, healthy	Studies not in HWE	*IL6* −174 (rs1800795), −572, −6331	PD in Caucasians: −174 (G allele OR: 1.24, CI: 1.01–1.51, GG *versus* GC + CC, OR: 1.39, 95% CI: 1.05–1.85)
Song et al. (2013) (South Korea)	Caucasian, Asian, Brazilian, Turkish, Indian, African	30	4915	3608	CP, AgP, healthy	nr	*TNF*-α −308 (rs1800629), −238 (rs361525), *IL6* −174 (rs1800795) and −572	PD in Brazilians: TNF-α −308 A allele (OR: 0.64, CI: 0.45–0.91) PD in Asians: TNF-α −308 A allele (OR: 0.40, CI: 0.20–0.71); PD in Turkish: TNF-α −308 A allele (OR: 1.82, CI: 1.04–3.19)

Table 1. (continued)

Authors and country	Separate analyses by ethnicity	No. studies included	Total number of cases	Total number of controls	Comparisons	Exclusions*	SNPs analysed	Significant associations
Ding et al. (2014) (China)	Caucasian, Asian	46	5186	6683	CP, AgP, healthy	"Systemic diseases"	*TNF*-α −308 (rs1800629), −238 (rs361525) and −863C/A (rs1800630)	AgP in Caucasians: TNF-α −308 AA *versus* AG + GA (OR: 1.84, CI: 1.15–2.95), A *versus* G allele (OR: 1.16, CI: 1.01–1.33) CP in Asians: TNF-α −308 AA *versus* AG + GA (OR: 2.39, CI: 1.49–3.82), A *versus* G allele (OR: 1.55, CI: 1.00–2.39); −238 G *versus* A allele (OR: 0.48, CI: 0.38–0.61); −863 AA *versus* CC/CA (OR: 2.20, CI: 1.08–4.46) AgP in Asians: TNF-α −308 AA *versus* AG + GA (OR: 2.75, CI: 1.12–6.75), A *versus* G allele (OR: 1.53, CI: 1.15–2.05)
Xie et al. (2012) (China)	Chinese	5	494	501	CP, AgP, healthy	nr	*TNF*-α −308 (rs1800629)	PD in Chinese: TNF-alpha-308 allele 2 (OR: 2.12, CI: 1.57–2.86, $p < 0.01$)
Jiang et al. (2012) (China)	Caucasian, Asian	8	628	717	CP, healthy	nr	*IL4* −590C/T	CP in Caucasians: −590 C *versus* T (OR: 0.71, CI: 0.56–0.89; CC *versus* CT + TT: OR: 0.61, CI: 0.42–0.88)
Yan et al. (2014) (China)	Caucasian, Asian, Brazilian	23	2361	3512	CP, AgP, healthy	nr	*IL4 590 C/T, 233 C/T and 70-Base-Pair*	PD in Caucasians: IL-4 −590 T allele (OR: 1.20, CI: 1.02–1.42) and TT genotype (OR: 1.68, CI: 1.05–2.67)
Chen et al. (2015) (China)	Caucasian, Asian, mixed Brazilian, African-American	12	2233	2655	CP, AgP, healthy	nr	*IL8* −251A/T (rs4073) and −845T/C (rs2227532)	PD in Brazilian mixed: −251 T *versus* A allele (OR: 0.80, CI: 0.68–0.94) PD in Asians: −251 T allele (OR: 1.17, CI: 1.03–1.33)

Table 1. (continued)

Authors and country	Separate analyses by ethnicity	No. studies included	Total number of cases	Total number of controls	Comparisons	Exclusions*	SNPs analysed	Significant associations
Albuquerque et al. (2012) (Portugal)	Caucasians, Han Chinese	9	841	748	CP, AgP, healthy	nr	*IL10* 1082 (rs1800896), 819 (rs1800871), 592 (rs1800872)	CP in Caucasians: IL10 −819 C *versus* T allele (OR: 1.48, CI: 1.01–2.17), −592 C *versus* A allele (OR: 1.72, CI: 1.17–2.54), CC *versus* AC + AA (OR: 0.44, CI: 0.27–0.72)
Zhong et al. (2012) (China)	Caucasian, Asian, Brazilian	14	1438	1303	CP, AgP, healthy	nr	*IL10* 1082 (rs1800896), 819 (rs1800871), 592 (rs1800872)	CP in Caucasians: IL10 819 C *versus* T allele (OR: 1.55, CI: 1.07–2.24)
Li et al. (2014) (China)	Caucasian, Asian	9	576	458	CP, AgP, healthy	Studies not in HWE	*IL18* −607A>C and −137G>C	PD in Caucasians: IL-18 −607 C *versus* A allele (OR: 1.86, CI: 1.30–2.65), AC + CC *versus* AA (OR: 2.64, CI: 1.34–5.21); −137 C *versus* G allele (OR: 1.47, CI: 1.13–1.91), GC + CC *versus* GG (OR: 1.66, CI: 1.21–2.29)
Ding et al. (2012) (China)	Caucasian, Asian	19	2011	1719	CP, AgP, healthy	"Systemic diseases"	*IL-1RN VNTR*	CP in Asians 2 *versus* L allele (OR: 1.82, CI: 1.31–2.54), L2/22 *versus* LL (OR: 2.12, CI: 1.44–3.11) AgP in Caucasians (2 *versus* L: OR: 0.59, 95% CI: 0.41–0.84, L2/22 *versus* LL: OR: 0.51, 95% CI: 0.33–0.77)
Jiang et al. (2014) (China)	Caucasian, Asian	6	2580	3073	CP, AgP, healthy	nr	*COX-2* −765G, −1195 and 8473	CP in Asians: −1195 A *versus* G allele (OR: 1.46, CI: 1.05–2.02; AA + AG *versus* GG (OR: 2.48, 95% CI: 1.35–4.53)
Prakash et al. (2015) (India)	Caucasian, Asian (Chinese, Indian)	4	1711	2402	CP, healthy	nr	*COX-2* (rs20417, rs689466 and rs5275)	CP in Chinese: rs20417 (CC + CG *versus* GG, OR: 0.55, CI: 0.38–0.78; C *versus* G allele: OR: 0.62, CI: 0.46–0.85)

Table 1. (continued)

Authors and country	Separate analyses by ethnicity	No. studies included	Total number of cases	Total number of controls	Comparisons	Exclusions*	SNPs analysed	Significant associations
Chen et al. (2012) (China)	Caucasian, Asian	18	Nr	nr	CP, AgP, healthy	SNPs not in HWE	*VDR*: TaqI (rs731236), BsmI (rs1544410), FokI (rs2228570) and ApaI (rs7975232)	CP in Asians: TaqI t allele (OR: 0.53, CI: 0.38–0.74); AgP in Asians: FokI f allele (OR: 1.58, CI: 1.16–2.17)
Deng et al. (2011) (China)	Caucasian, Asian	15	1338	1302	CP, AgP, healthy	nr	*VDR*: TaqI (rs731236), BsmI (rs1544410), FokI (rs2228570) and ApaI (rs7975232)	None (only with high heterogeneity)
Chrzeszczyk et al. (2015) (Poland)	Caucasian	14	1621	1755	CP, AgP, healthy	Incomplete genotype, unclear definitions, no information on genotyping, significant demographic differences between groups	*TLR4*: Asp299, Thr399Ile	CP in Caucasians: Asp299 Gly (OR: 1.35, CI: 1.02–1.8; $p = 0.038$)
Ozturk & Vieira (2009) (USA)	Caucasian, Asian, Brazilian	7	1039	1311	CP, AgP, healthy	Studies with incomplete genotyping	*TLR4:* Asp299Gly, Thr399Il	CP in Caucasians: Asp299Gly (OR: 1.43, CI: 1.04–1.97; $p = 0.03$)
Zheng et al. (2013) (China)	Asian and non-Asian	15	1728	1797	CP, AgP, healthy	nr	*TLR4* Asp299Gly and *Thr*399Il	None
Han et al. (2015) (China)	Caucasian, Asian, African	32	5864	6929	CP, AgP, healthy	nr	*CD14* −260 (rs2569190), *TLR2* 2408 (rs5743708), *TLR4* 896 (rs4986790) and 1196 (rs4986791), *MBL* 54 (rs1800450)	CP in Caucasians: TLR4 869 G allele (OR: 1.32, CI: 1.04–1.68); CP in Caucasians: TLR4 1196 mutant allele (OR: 1.37, CI: 1.05–1.80)
Song et al. (2013) (South Korea)	Caucasian, Asian, Turkish	32	5295	5354	CP, AgP, healthy	nr	*TLR2* Arg753Gln, *TLR4* Asp299Gly, *Thr*399Ile, *MMP-1* −1607 (rs1799750) and *MMP-9* −1562	None

Table 1. (continued)

Authors and country	Separate analyses by ethnicity	No. studies included	Total number of cases	Total number of controls	Comparisons	Exclusions*	SNPs analysed	Significant associations
Ding et al. (2015) (China)	Caucasian, Asian, Brazilian	7	1213	1831	CP, AgP, healthy	nr	*MMP3* −1171 (rs35068180)	PD in Asians: 6A allele *versus* 5A allele (OR: 0.68, CI: 0.58–0.80); 5A/6A + 6A/6A *versus* 5A/5A (OR: 0.51, CI: 0.39–0.66); CP in Caucasians: 6A allele *versus* 5A allele (OR: 0.66, CI: 0.44–0.97); CP in mixed Brazilians: 5A/6A + 6A/6A *versus* 5A/5A (OR: 0.31, CI: 0.13–0.76)
Hou et al. (2013) (China)	Caucasian, Asian	11	1447	1710	CP, AgP, healthy	nr	*MMP1* −1607 1G/2G (rs1799750)	None (only with high heterogeneity)
Li et al. (2013) (China)	Caucasian, Asian	11	1580	1386	CP, AgP, healthy	nr	*MMP1* −1607 (rs1799750)	None
Li et al. (2013) (China)	Caucasian, Asian, Brazilian	8	1001	897	CP, AgP, healthy	Studies not in HWE	*MMP1* −1607 (rs1799750)	None
Pan et al. (2013) (China)	Caucasian, Asian	7	1317	628	CP, AgP, healthy	nr	*MMP9* −156	PD in Caucasians CT-TT *versus* CC (OR: 0.61, CI: 0.46–0.81), TT *versus* CT-CC (OR: 2.87, CI: 1.14–7.17)
Zhang et al. (2013) (China)	No specific ethnicity assessed	8	934	877	CP, AgP, healthy	nr	*CD14* −159	None
Zheng et al. (2013) (China)	No specific ethnicity assessed	8	1228	1116	CP, AgP, healthy	nr	*CD14* −159 and −260	None
Dimou et al. (2010) (Greece)	Caucasian, Asian	17	1685	1570	CP, AgP, healthy	nr	*Fc-γR*: IIA H131R (rs1801274), IIIA 158V (rs396991) and IIIB NA1/NA2	None
Song et al. (2013) (South Korea)	Caucasian, Asian, African	25	1421	1454	CP, AgP, healthy	nr	*Fc-γR*: IIA H131R (rs1801274), IIIA 158V (rs396991) and IIIB NA1/NA2	PD in Caucasians: Fc-γIIA RR/RH *versus* HH (OR: 0.62, CI: 0.48–0.81, $p < 0.001$); Fc-γIIIA V allele (OR: 1.46, CI: 1.01–2.09, $p = 0.042$)
Huang et al. (2015) (China)	Caucasian, Asian	11	nr	nr	CP, AgP, healthy	nr	*TGF-b1* 509C/T (rs1800469), +869T/C (rs1800470) and +915G/C (rs1800471)	CP in Asians: TGF-b1 509 T allele (OR: 0.81, CI: 0.69–0.97)

Table 1. (continued)

Authors and country	Separate analyses by ethnicity	No. studies included	Total number of cases	Total number of controls	Comparisons	Exclusions*	SNPs analysed	Significant associations
Stein et al. (2008) (Germany)	Caucasian	12	nr	nr	CP, AgP, healthy	Unclear dx, CP studies with reference controls, inappropriate data presentation	*HLA*	AgP in Caucasians: HLA-B15 (OR: 1.90, CI: 1.15–3.16, $p = 0.01$); HLA-A2 (OR: 0.72, CI: 0.56–0.94, $p = 0.01$); HLA-B5 (OR: 0.49, CI: 0.30–0.79, $p = 0.004$)
Weng et al. (2015) (China)	Chinese	7	1408	1574	CP, AgP, healthy	nr	*Oestrogen Receptor-α XbaI* (rs9340799) and *PvuII* (rs2234693)	None

AgP, aggressive periodontitis; CI, 95% confidence intervals; CP, chronic periodontitis; dx, diagnosis; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; PD, periodontitis (AgP and CP grouped together or not specified).
Only associations significant after multiple testing are reported. Associations with "disease severity" are not reported owing to heterogeneity of definitions. Associations for mixed ethnicities grouped together are not reported. Only dominant *versus* recessive models and allele comparisons reported (no associations between homozygosity for the wild allele *versus* homozygosity for the mutant allele). Associations after multivariate analysis are presented when available (results of univariate analysis not confirmed by multivariate are not reported). Only results with low or moderate heterogeneity were reported, based on I^2 test < 50% or $p < 0.10$ (Higgins et al. 2003).
*Inclusions for all reviews were studies reporting data on single-nucleotide polymorphism (SNP) allele/genotype distribution between periodontitis and healthy subjects.

et al. 2011). A gene-centric GWAS identified a nominal association between the *VDR* gene and presence of CP in Caucasians (Rhodin et al. 2014) and a separate GWAS in a Japanese population identified an association between SNP rs2853564 in the VDR gene and periodontitis (Shimizu et al. 2015).

- *Fc-γRIIA* gene: The *Fc-γRIIA* (rs1801274) was associated in Caucasians with CP in a systematic review and meta-analysis (Song & Lee 2013), and a nominal association was found in a Japanese GWAS (Shimizu et al. 2015).
- Interleukin-10 (*IL10*) genes SNPs in the *IL10* gene (rs1800871 and rs1800872) were associated with periodontitis in CGS and the association was confirmed in systematic reviews and meta-analyses in Caucasians (Albuquerque et al. 2012, Zhong et al., 2012). Different SNPs in the same gene (rs6667202 and rs61815643) were associated with periodontitis in a large study including a pooled German-Austrian AgP sample and a Dutch AgP sample (Schaefer et al. 2013).

Several genes and SNPs with moderate evidence of association with periodontitis were detected in various systematic reviews, in different ethnic populations (see Table 5 for details). Weaker evidence for associations, according to the criteria defined a priori was detected for SNPs in the following genes in different populations (see Table 5 for details).

Association with caries

Reviewing studies reporting associations between genetic variants and caries, some promising genes emerged with associations replicated in multiple population cohorts by multiple independent studies (see Table 6). The most replicated result for caries is the association with genetic variants in or flanking amelogenin. However, the strongest evidence for a role of amelogenin in the individual susceptibility to caries is the corroborating functional data that show transgenic mice with different levels of expression of

Table 2. Summary of periodontal candidate gene studies including at least 1000 subjects and not included in the systematic reviews above

Authors and country	Ethnicity	Total number of cases	Total number of controls	Replication sample	Genetic analysis	SNPs studied	Significant associations
de Jong et al. (2014) (Germany-Holland)	Caucasian	283 (AgP)	979 (578 population representative, 401 blood donors)	AgP $n = 417$, CP $n = 1359$, representative controls $n = 1360$, PD-free individuals $n = 552$, controls (for CP cases) $n = 506$	Affymetrix 500K genotyping arrays; TaqMan genotyping system for SNP rs6596473	Genetic regions of SLC23A1 and SLC23A2	AgP stage 1: rs6596473 in SLC23A1 ($p = 0.026$, OR 1.26) and AgP pooled (674 cases, 2891 controls) ($p = 0.005$, adjusted OR = 1.35) Stage 2: no association with other AgP samples Stage 3: no association with severe CP
Folwaczny et al. (2011) (Germany)	Caucasian	389	771	None	PCR amplification and fragment analysis	MHC class I chain-related gene A (MICA)-TM exon 5 trinucleotide polymorphism, the MICB-C1_2_A intron 1 dinucleotide polymorphism and the tetranucleotide polymorphism C1_4_1	PD (males): MICA-TM allele A5 ($p = 0.0001$, OR: 2.17, CI: 1.55–3.03) C1_4_1 allele ($p = 0.006$; OR: 0.74, CI: 0.60–0.91) Two haplotypes (MICA:A5-C1_4_1:5; $p = 0.002$, OR: 2.63, CI: 1.46–4.74 and MICB:CA16-C1_4_1:3; $p = 0.014$; OR: 0.68, CI: 0.50–0.92)
Folwaczny et al. (2012) (Germany)	Caucasian	402	793	None	PCR and melting curve analysis with FRET probes	NR1I2 (PXR)-encoding gene (rs12721602, rs3814055, rs1523128, rs1523127, rs45610735, rs6785049, rs2276707 and rs3814057)	Haplotype (GTGAG) of rs12721602, rs3814055, rs1523128, rs12721607 and rs6785049 (adjusted $p = 0.011$, OR: 0.46, CI: 0.25–0.84)

Table 2. (continued)

Authors and country	Ethnicity	Total number of cases	Total number of controls	Replication sample	Genetic analysis	SNPs studied	Significant associations
Kallio et al. (2014) (Finland)	Caucasian	Parogene 1 $n = 89$ advanced PD	Parogene 1 $n = 64$ no advanced PD	Parogene 2 $n = 339$ and Health 2000 Survey ($n = 1420$)	Illumina 610K genotyping chip	(MHC) polymorphisms (6p21.3)	Haplotype of SNPs, rs11796, rs3130059, rs2239527,rs2071591, rs909253 and rs1041981 (genes *BAT1*, *NFKBIL1* and *LTA*): association with PPD > 6 mm (OR: 2.90, CI: 2.37–3.52) and severe PD (OR: 3.10, CI: 1.63–5.98 (confirmed in both replication samples)
Schaefer et al. (2009) (Germany)	Caucasian	151 GAgP	736	137 LAgP, 368 controls	SNPlex and TaqMan GenotypingSystem	ANRIL gene, SNPs rs2891168, rs1333042 and rs1333048	GAgP: rs1333048 recessive model OR: 1.99, CI: 1.33–2.94; $p = 0.0006$ LAgP: rs1333048 recessive model OR: 1.72, CI: 1.06–2.76, $p = 0.027$
Schaefer et al. (2013) (Germany-Holland)	Caucasian	600 AgP	1448 population representative	AgP $n = 136 + 155 + 49 + 93$, CP $n = 1437$, controls $n = 581 + 341 + 679 + 103 + 75 + 1125$	Illumina custom genotyping array Immunochip	23 genes: ABO, CCR5, FCGR2A, FCGR2C, FCGR3A, FCGR2B, FCGR3B, IL1B, IL2, IL6, IL10, LTA, MMP9, NOD2, TLR2, TLR4, VDR, CD14, IL1A, IL1RN, TNFRSF11B (OPG), IFNGR1, L-selectin + ANRIL (only in subset)	Pooled German-Austrian AgP sample: IL10 rs6667202 ($p = 0.016$, OR: 0.77, CI: 0.6–0.95); Dutch AgP sample: adjacent IL10 SNP rs61815643 ($p = 0.0009$, OR: 2.31, CI: 1.4–3.8) Turkish sample: ANRIL rs1333048 ($p = 0.026$, OR: 1.67, CI: 1.11–2.60)

Table 2. (continued)

Authors and country	Ethnicity	Total number of cases	Total number of controls	Replication sample	Genetic analysis	SNPs studied	Significant associations
Shang et al. (2015) (China)	Han Chinese	471	1312	793 cases, 2489 controls	Sequenom MassARRAY matrix-assisted laser desorption ionization-time of the flight mass spectrometry platform	FBXO38, AP3B2 and WHAMM genes	*FBXO38* (rs10043775, $p = 0.0009$) Haplotype CA from *AP3B2* (rs11631963-rs11637433): $p = 0.0001$; haplotype ATC of rs1864699-rs2099259-rs2278355, $p = 3.84 \times 10^{-8}$)
Zhang et al. (2014) (China)	Han Chinese	400	750	None	MassARRAY platform with iPLEX GOLD chemistry	23 SNPs in IL8 gene	CP: rs4073 TT genotype (adjusted OR: 1.45, CI: 1.20–1.63, $p = 0.017$) and rs2227307 T allele (adjusted OR: 1.60, CI: 1.21–1.98, $p = 0.029$) haplotype block (rs4073-rs2227307-rs2227306)

AgP, aggressive periodontitis; CI, 95% confidence intervals; CP, chronic periodontitis; FRET, fluorescence resonance energy transfer; GAgP, generalized aggressive periodontitis; LAgP, localized aggressive periodontitis; OR, odds ratio; PCR, polymerase chain reaction; PD, periodontitis (AgP and CP grouped together or not specified); SNP, single-nucleotide polymorphism.

amelogenin during dental development directly correlating with variable enamel microhardness (the higher the levels of amelogenin during dental development, the harder the enamel). Indeed, enamel formed with lower levels of amelogenin was more susceptible to acidic demineralization (Vieira et al. 2015a,b). Other promising results warrant further experimentation to unveil mechanisms: aquaporin 5 (Anjomshoaa et al. 2015); ESRRB (Weber et al. (2014); and rs7791001 in 7q22.3 (Sofer et al. 2016), which show the application of genomics to caries is moving from its infancy.

Genetic variants associated with both caries and periodontal diseases

Genes and SNPs emerging as having "strong," "moderate" or "weak" evidence of association with periodontitis (Table 5) were compared with genes associated with caries (Table 4). None of the variants were shown to be conclusively associated with both caries and periodontal disease. Only one of the reviewed studies included analysis of the same genetic variants of the beta defensin gene (*DEFB1*) for both diseases (Ozturk et al. 2010) but the results suggested an association with caries and not with periodontal diseases. The association between *DEFB1* and caries was detected in an independent study (Krasone et al. 2014) but not in another (Bin Mubayrik et al. 2014), whereas an association was detected for a gene variant in the *DEFB1* with periodontitis in a GWAS (Shimizu et al. 2015). Other genes that have been studied for both diseases in independent studies include *ACE*, *CD14*, *MMP2*, *MMP9*, *MMP13* and variants in the HLA loci. The insertion/deletion polymorphism in the *ACE* gene (intron 16) was associated with serum ACE levels (Rigat et al. 1990) and was shown to be associated with caries [although the two studies we found are contradictory with one suggesting a protective effect for the DD genotype, whereas the other suggests the opposite effect (Olszowski et al. 2015, Linhartova et al. 2016)]. The same *ACE* polymorphic variant was independently studied for CP and the studies showed the same discrepancy on protecting *versus*

Table 3. Summary of characteristics and main results of reviewed genome-wide association studies (GWAS)

Authors and country	Ethnicity	Total number of cases	Definition of case	Total number of controls	Definition of control	Replication sample	Genetic analysis	Exclusions, number of SNPs	Significant associations	Other results
Divaris et al. (2012) (USA)	Caucasian	2681	Eke 2007	1823	Mild- no PD (Eke 2007 criteria)	Health ABC (n = 656)	Affymetrix Genome-wide Human SNP Array 6.0 chip	669,450 (excluded HWE) $p < 10^{-5}$, call rate <95%, quality score < 0.8, missing data rate < 10% after imputation and MAF of <5%)	None at $p < 0.5*10^{-8}$	5×10^{-6} threshold: 26 SNPs in 6 loci: NIN, NPY, WNT5A for severe CP and NCR2, EMR1, 10p15 for moderate CP; NPY rs2521634 nominal association in replication (severe CP); 3 SNPs (rs2521634, rs7762544 and rs3826782) confirmed association with severe CP in meta-analysis with replication sample
Feng et al. (2014) (USA)	Caucasian, Black	99	≥30% sites ≥5 mm CAL	767	ns	2 cohorts from Brazil	SNP array for European and African ancestry	473,514 (excluded monomoprhic and missing rate >10%, no HWE, MAF < 0.05)	None at $p < 0.1*10^{-7}$	1E-05/06 for 20 suggestive loci (of which 12 intergenic)
Freitag-Wolf et al. (2014) (Germany)	Caucasian (German)	329	AgP: ≥2 teeth with 50% bone loss and <35 years age	983	Popgen biobank: population representative individuals from Kiel region (N = 500) and blood donors from Kiel (N = 500)	German'-Austrian 382 AgP/489 population controls	Affymetrix Gene Chip Human Mapping 500K Array Set (TaqMan assay for replication)	Genotype call rate < 90%, MAF > 5%, no HWE	NPY rs198712: $p = 5.4 \times 10^{-6}$ for the sex interaction and $p = 9.8 \times 10^{-6}$ and $p = 0.0240$ for SNP and sex respectively	rs1477403 on 16q22.3 and 3 SNPs 21q22.11: trend for association in replication and meta-analysis

Table 3. (continued)

Authors and country	Ethnicity	Total number of cases	Definition of case	Total number of controls	Definition of control	Replication sample	Genetic analysis	Exclusions, number of SNPs	Significant associations	Other results
Hong et al. 2015 (South Korea)	Korean	414 (moderate-severe PD)	Eke et al. (2012)	263 (health and mild PD)	Mild-no PD (Eke et al. 2012)	–	Illumina Human 1M-duo Beadchip	Genotype accuracy <98%, ≥4% missing genotype call rate, >30% heterozygosity, inconsistency in sex, MAF < 0.01, no HWE	None at $p < 0.5*10^{-8}$	Suggestive associations: TENM2 moderate PD, LDLRAD4 severe PD
Rhodin et al. (2014) (USA)	Caucasian	2681	Eke 2007	1823	Mild- no PD (Eke 2007 criteria)	Health ABC ($n = 656$)	Affymetrix Genome-wide Human SNP Array 6.0 chip	Missing data >10%, MAF < 5%, imputation quality score < 0.8	Genes NIN, ABHD12B, WHAMM, AP3B2 associated with severe CP	Genes HGD, ZNF675, TNFRSF10C and EMR1 had suggestive associations with moderate CP; nominal associations for previously studied genes VDR, TNFSF14, GADD45B and VAV1
Schaefer et al. (2010) (Germany)	Caucasian (German)	141 GAgP + 142 LAgP	Rep in Schaefer 2009	500 + 479	Popgen biobank: population registry, Germany ($n = 500$) for stage 1 and Blood Service of the University Hospital Schleswig-Holstein ($n = 472$) for stage 2	164 case individuals of ≤35 years of age and 368 ethnically and age-matched healthy controls	Affymetrix Gene Chip Human Mapping 500K Array Set (except controls of GWAS2, genotyped with Affymetrix Gene Chip 5.0)	Genotype call rate <90% and a MAF > 5%, no HWE	GLT6D1 (rs1537415) G allele: GAgP ($p = 1.8 \times 10^{-4}$, OR: 1.67, CI: 1.27–2.18); LAgP ($p = 3.1 \times 10^{-4}$, OR: 1.65, CI: 1.26–2.17)	GLT6D1 rs1537415: $p = 5.7 \times 10^{-3}$, OR: 1.47, CI: 1.12–1.93 in replication and $p = 5.51 \times 10^{-9}$, OR: 1.59, CI: 1.36–1.86 in meta-analysis with replication sample
Schaefer et al. (2015) (Germany)	Caucasian	703	≥2 teeth with 50% alveolar bone loss under the age of 35 years	2143	Various	159 Dutch AgP and 679 Dutch population representative	18 CAD risk loci with Affymetrix 500K arrays + Immunochip + TaqMan for SNP rs1981458 and rs17514846 (FURIN), rs4252120 (PLASMINOGEN) and rs2679895 (TGFBRAP1)	Genotype call rate <90% and a MAF > 5%, no HWE	TGFBRAP1 rs2679895: assoc. with AgP ($p = 0.0016$,OR: 1.27, CI: 1.1–1.5) and CAD ($p = 0.0003$, OR: 0.84, CI: 0.8–0.9)	ANRIL and PLG gene confirmed in candidate gene analysis; TGFBRAP1 rs2679895 confirmed but in opposite direction in replication sample

Table 3. (continued)

Authors and country	Ethnicity	Total number of cases	Definition of case	Total number of controls	Definition of control	Replication sample	Genetic analysis	Exclusions, number of SNPs	Significant associations	Other results
Shaffer et al. (2014) (USA)	Caucasian (non-Hispanic)	93 (for more severe definition)	PPD>5 mm in >1 sextant or previous gum surgery (PD1 and PD2 definitions depending on missing teeth)	529	No PPD>5 mm in >1 sextant or previous gum surgery		Illumina Human610-Quadv1_B BeadChip	Not specified (excluded no HWE and MAF < 0.02)	None at $p < 0.5*10^{-8}$	10 suggestive loci (17 SNPs) with *p*-values between 1E-5 and 1E-7; nominal associations for previously reported genes CAMTA1, RUNX2 and ETS
Shimizu et al. (2015) (Japan)	Japanese	1593	Unclear	7980	1 of 5 diseases (cerebral aneurysm, oesophageal cancer, endometrial cancer, COPD or glaucoma) + 1023 + 906 healthy volunteers; no history of PD (based on questionnaire)	1167 Cases + 7178 Controls from BioBank Japan with 1 of 5 diseases (epilepsy, urolithiasis, nephrotic syndrome, atopic dermatitis or Graves' disease)	Illumina HumanOmni Express BeadChip	597,434 in autosomal chromosomes (excluded call rate <99%, no HWE, MAF < 0.01, closely related pair samples)	None at $p < 0.5*10^{-8}$	$p < 5 \times 10^{-4}$ for 250 independent SNPs; nominal association in 6 previously reported genes: FCGR2A (rs1801274), IL1RN (rs315920), VDR (rs2853564), CDKN2BAS (rs1333042), DEFB1 (rs1047031) and PTGS2 (rs5277); meta-analysis with replication sample: significant associations for KCNQ5 rs9446777 and GPR141-NME8 rs2392510

Table 3. (continued)

Authors and country	Ethnicity	Total number of cases	Definition of case	Total number of controls	Definition of control	Replication sample	Genetic analysis	Exclusions, number of SNPs	Significant associations	Other results
Teumer et al. (2013) (Germany)	Caucasian	1916	4 definitions: (i) mean PAL, (ii) % PAL ≥ 4 mm, (iii) Page and Eke 2007 definition and (iv) 5-year change in mean PAL	1816	Depending on 4 disease definitions	No replication (SHIP and SHIPtrend analysed together)	Affymetrix Genome-Wide Human SNP Array 6.0 or the Illumina Human Omni 2.5 array + Illumina Human Omni 2.5 array	905,910 and 1,824,743 SNPs were used for imputation in SHIP and SHIP-TREND. 17,533,349 and 17,585,496 markers in SHIP and SHIP-TREND including about 1.1 million short INDELs (excluded no HWE, low call rates, SNPs which could not be mapped, monomorphic; MAF ≤ 5% and low imputation quality)	None	No association for previously reported SNPs; adjusted variance explained by additive effects of all common SNPs was 23% and 14% depending on definitions

AgP, aggressive periodontitis; CP, chronic periodontitis; CPAL, proximal attachment loss; HWE, Hardy–Weinberg equilibrium; MAF, minimum allele frequency; OPD, chronic obstructive pulmonary disease; PD, periodontitis; PPD, probing pocket depth; SHIP, study of health in pomerania; SNP, single-nucleotide polymorphism.

increasing risk (Hollá et al. 2001, Gürkan et al. 2009, Kang et al. 2015). CD14 was absent in the saliva of individuals with active caries lesions (Bergandi et al. 2007) and no associations were confirmed with the periodontitis trait (Zhang et al., 2013, Zheng et al., 2013, Han et al. 2015). The HLA locus showed certain alleles associated with individuals with periodontitis (Stein et al. 2008) and separately with caries (Lehner et al. 1981, Altun et al. 2008, Bagherian et al. 2008, Valarini et al. 2012), but at least one study did not find an association with caries (de Vries et al. 1985). Gene variants in the matrix metalloproteinase (MMP) 13 showed association with caries, whereas *MMP2* and *MMP9* were not associated with caries (Tannure et al. 2012a). Some evidence of association between SNPs in the *MMP*9 gene and periodontitis were shown in a systematic review (Pan et al. 2013).

Discussion

This is the first systematic review to investigate associations between host genetic variants and both caries and periodontal disease. The large literature on periodontal genetics was systematically investigated to detect relevant genes and then cross-references to the less large evidence on genetics of caries. Associations between gene variants and both diseases can be sought with two possible approaches: (i) hypothesis-testing (usually employing a candidate gene approach) and (ii) hypothesis-generating (usually with the use of GWAS). Attempts to appraise host genetic variants associated with periodontitis had been made in recent years. Laine et al., by reviewing existing association studies, suggested some SNPs as possibly predisposing to AgP and CP, although none of them had been unequivocally associated with periodontitis. They highlighted the need for stringent case definition, recruitment of ethnically homogeneous subjects and for large sample sizes (Laine et al. 2012). Another study used text mining to prioritize candidate genes from GWAS and studies on expression profiles, resulting in 21 genes identified by different bioinformatics tools as the most promising genes. Some of these genes – namely *IL18*,

Table 4. Summary of study design and rationale for genetics of caries studies included in this review

Study design	Genes	Rationale	References
Candidate genes	Enamel formation genes (*AMELX*, *ENAM*, *AMBN*, *TUFT1*, *TFIP11*, *MMP20*, *KLK4*)	The general assumption is that genetic variation in genes involved in enamel formation may lead to a structure that is more susceptible to demineralization	Slayton et al. (2005), Deeley et al. (2008), Patir et al. (2008), Olszowski et al. (2012), Shimizu et al. (2012), Tannure et al. (2012b), Wang et al. (2012b), Gasse et al. (2013), Jeremias et al. (2013), Antunes et al. (2014), Chaussain et al. (2014), Duverger et al. (2014), Ergöz et al. (2014), Halusic et al. (2014), Abbasoğlu et al. (2015), Bayram et al. (2015), Hu et al. (2015), Ohta et al. (2015), Romanos et al. (2015), Saha et al. 2015, Shaffer et al. (2015)
	Immune response genes (*ACE, CD14*, HLA locus, *DEFB1*, *LTF*, *MUC7*, *MBL2*, *MASP2*)	Since caries is a bacteria-mediated disease, the assumption is that genetic variation in immune response/inflammatory genes could influence cariogenic and/or non-cariogenic biofilm formation	Lehner et al. (1981), Bergandi et al. (2007), Altun et al. (2008), Bagherian et al. (2008), Azevedo et al. (2010), Ozturk et al. (2010), Brancher et al. (2011), Pol (2011), Buczkowska-Radlińska et al. (2012), Olszowski et al. (2012), Valarini et al. (2012), Fine et al. (2013), Yang et al. (2013), Bin Mubayrik et al. (2014), Krasone et al. (2014), Mauramo et al. (2014), Abbasoğlu et al. (2015), Doetzer et al. 2015, Olszowski et al. (2015), Linhartova et al. (2016), Yildiz et al. (2016)
	Saliva-related genes and Proteins (*AQP5*, *PRH1*, sortase A, *CA6*)	Genetic variation influencing saliva amount and composition may influence caries susceptibility in multiple ways (i.e. modulating acid buffering capacity, influencing cariogenic and non-cariogenic biofilm formation)	Zakhary et al. (2007), Yarat et al. (2011), Wang et al. (2012b), Anjomshoaa et al. (2015), Li et al. (2015), Yu et al. (2015), Sengui et al. (2016), Yildiz et al. (2016)
	Other genes (*BMP2*, *MMP2*, *MMP9*, *MMP13*, *TIMP2*, *TAS2R38*, *TAS1R2*, *GNAT3*, *SLC2A2*, *DSPP*, *SPP1*, *CA4*)	Genes involved in collagen metabolism, mineralization and dietary preferences have been selected as candidates for caries	Wendell et al. (2010), Tannure et al. (2012a), Wang et al. (2012b), Kulkarni et al. (2013), Abbasoğlu et al. (2015), Hollá et al. (2015), Yildiz et al. (2016)
Linkage	Low caries experience: 5q13.3, 14q11.2, Xq27.1; high caries experience: 13q31.1, 14q24.3)	The first genome-wide study for caries used a linkage design and identified five loci, three for low caries experience and two for higher caries experience. These analyses were based on a severity of caries experience scheme based on DMFT scores. The strongest evidence from these studies supports a role of *ESRRB*, possibly related to enamel resistance to demineralization	Original genome-wide linkage study: Vieira et al. (2008) Follow-up fine mapping studies: Briseño-Ruiz et al. (2013), Küchler et al. (2013), Shimizu et al. (2013), Küchler et al. (2014), Weber et al. (2014)
Association (GWAS)	Primary dentition: 1p34, 1q42-q43, 6q16.1, 11p13, 17q23.1, 22q12.1; permanent dentition: 1p36, 2p24, 2q35, 4p15, 4q22, 4q31.22, 4q32, 5q11. 1, 6q27, 7p15-13, 7q21, 7q22, 7q22.3, 8q21.3, 10p11.23, 14q22, 17q11, Xp11.4, Xq26.1)	GWAS for caries attempted to compare caries free with caries affected individuals, based on caries experience measured by dmft/DMFT scores. A number of genes/loci have been suggested as associated. The phenotype has been redefined based on location of lesions and other schemes and overall the results are inconclusive	First studies for the primary and permanent dentitions: Shaffer et al. (2011), Wang et al. (2012a) Follow-up fine mapping and reanalysis of the initial studies and additional GWAS from others: Shaffer et al. (2013), Wang et al. (2013), Zeng et al. (2013), Stanley et al. (2014), Zeng et al. (2014), Morrison et al. (2016), Sofer et al. (2016)

DMFT, decayed-missing-filled teeth; GWAS, genome-wide association study.

Table 5. Summary of evidence for association between genes and outcome "periodontitis"

Evidence level	First line of evidence	Second line of evidence	Third line of evidence	Genes/SNPs
Strong	Robust GWAS	Independent GWAS or robust CGS	Good-quality SR	None
	CGS	Good quality SR	GWAS (at least nominal association) or independent robust CGS	CP: *VDR* (Chen et al. 2012, Rhodin et al. 2014, Shimizu et al. 2015)*
				CP: *Fc-γRIIA* (rs1801274) (Song & Lee 2013, Shimizu et al. 2015)†; *IL10* (Albuquerque et al. 2012, Zhang et al. 2012, Schaefer et al. 2013)‡
Moderate	Robust GWAS	Independent GWAS or robust CGS	None	None
	CGS	Good-quality SR	None	CP in Caucasians: *TLR4* (Chrzeszczyk et al. 2015), *TNF-α* (Ding et al. 2014), *IL1A* (Nikolopoulos et al. 2008, Karimbux et al. 2012, Mao et al. 2013), *IL1B* (Deng et al. 2013), *IL4* (Jiang 2012, Yan 2014), MMP9 (Pan et al. 2013) AgP in Caucasians: *IL1VNTR* (Ding et al. 2012), *HLA* (Stein et al. 2008) CP Asians: *COX2* (Jiang et al. 2014), *TNF-α* (Ding et al. 2014), *IL1B* (Nikolopoulos et al. 2008, Ma et al. 2015), *IL1VNTR* (Ding et al. 2012), *IL8* (Chen et al. 2015), *TGF-b* (Huang et al. 2015) AgP Asians: *TNF-α* (Ding et al. 2014) PD Brazilians: *IL8* (Chen et al. 2015)
	Robust CGS	Other CGS or replication sample in same study	None	AgP in Caucasians: *ANRIL* (Schaefer 2009, 2013), *SLC23A1* and *SLC23A2* (de Jong et al. 2014) CP in Caucasians: *MHC* (Kallio et al. 2014) CP in Asians: *FBXO38* (Shang et al. 2015)
Weak	Robust GWAS	None	None	AgP in Caucasians: *NPY* (Freitag-Wolf et al. 2014), *GLT6D1* (Schaefer et al. 2010), *TGFBRAP1* (Schaefer et al. 2015)
	GWAS (suggestive association)	Independent GWAS (suggestive association) or CGS	None	CP in Asians: *CDKN2BAS, DEFB1, PTGS2* (Shimizu et al. 2015) PD in Caucasians: *CAMTA1, RUNX2* (Divaris et al. 2013, Shaffer et al. 2014), *ETS* (Divaris et al. 2013, Teumer et al. 2013)
	Robust CGS	None	None	CP in Caucasians: *MICA-TM* (Folwaczny et al. 2011), *NR1I2* (Folwaczny et al. 2012)
	CGS	SR (modified AMSTAR score ≤ 4)	None	CP in Caucasians: *IL18* (Li et al. 2014), *IL6* (Shao et al. 2009)

CGS, candidate gene study; CP, chronic periodontitis; GWAS, genome-wide association study; PD, periodontitis; SNP, single-nucleotide polymorphism; SR, systematic review.
Definition of robust GWAS: GWAS wit independent replication and quality score > 10 (Nibali 2013).
Definition of robust CGS: CGS including at least 1000 subjects and with quality score > 10 (Nibali 2013).
Definition of good-quality systematic review/meta-analysis: modified AMSTAR score > 4.
*Different SNPs in the study by Shimizu et al. Gene-centric analysis in the study by Rhodin et al.
†Observed in different populations: Caucasian (Song et al. 2013)/Asian (Shimizu et al. 2015).
‡Different forms of disease (CP *versus* AgP) and different SNPs.

[*Correction added on 20 March 2017, after first online publication. In table 5, references Song et al. 2013, was changed to Song & Lee 2013 and Rhodin et al. 2013 was changed to Rhodin et al. 2014*].

IL6ST (interleukin 6 signal transducer), *CD44*, *CXCL1* [chemokine (CXC motif) ligand 1], *MMP3*, *MMP7*, *MMP13*, *CCR1* [chemokine (C–C motif) receptor 1] and *TLR9* – have been suggested in previous studies, whereas the others have not been previously associated with periodontitis (Zhan et al., 2014).

To have an evidence-based summary of predisposing gene variants, we set some criteria for strength of evidence for association with the "periodontitis" phenotypes (Appendix S4). These criteria are based purely on disease association in systematic reviews, large CGS and GWAS, with no aim to investigate functional relevance, gene expression or potential epigenetic changes. Based on these criteria, SNPs in the Vitamin D Receptor (*VDR*), the *Fc-γRIIA* and the Interleukin-10 (*IL10*) genes emerged as associated with periodontitis with "strong" level of evidence. However, associations within these genes were often observed for different SNPs and/or in different populations. Therefore, further research needs to be conducted to clarify the SNPs with strongest disease associations in these genes and the strength of association in the different populations. Moderate evidence of association was detected for SNPs in several genes, including the most-researched interleukin 1 (*IL1-alpha* and *IL1-beta*) genes.

The literature on genetic associations for caries is smaller than the one for periodontitis. Therefore, we identified all published candidate

Table 6. Summary of the most promising results of association with caries

Gene	Rationale	Evidence	Functional analyses	References
Amelogenin (*AMELX*)	Inactivating mutations cause X-linked amelogenesis imperfecta and hypomorphic alleles may lead to higher susceptibility to caries due to formation of enamel more vulnerable to acid demineralization	Association replicated in multiple population cohorts by multiple independent studies	Enamel microhardness of transgenic mouse models teeth formed under varied levels of amelogenin correlate with levels of gene expression. Enamel microhardness of human teeth is associated with *AMELX*	Deeley et al. (2008), Patir et al. (2008), Shimizu et al. (2012), Vieira et al. (2015a,b)
Aquaporin 5 (*AQP5*)	Knockout mice have very viscous saliva and are suggested to be a good model to study caries	Association replicated in multiple population cohorts by multiple independent studies	Higher levels of aquaporin 5 expression in human whole saliva are associated with less caries experience. Aquaporin 5 may interact with fluorides	Wang et al. (2012b), Anjomshoaa et al. (2015)
Estrogen Receptor Related Beta (*ESRRB*)	Located in the locus 14q24.3, which was linked to caries through a genome-wide linkage scan	Association replicated in multiple populations	Mutations in *ESRRB* cause congenital forms of hearing impairment and families carrying mutations have substantial higher caries experience and tooth loss. Enamel microhardness of human teeth is associated with *ESRRB*	Vieira et al. (2008), Weber et al. (2014)
rs7791001 (7q22.3)	Marker was associated with caries when the Hispanic origin was considered	Meta-analysis of multiple genome-wide association studies	rs7791001 is located in a cluster of DNAseI hypersensitivity derived from assays in 95 cell types, as part of the ENCODE project. Regulatory regions in general, and promoters in particular, tend to be DNAse-sensitive	ENCODE Project Consortium (2004); Sofer et al. (2016)

gene and genome-wide studies to date to caries (Table 4). Three genes, *AMELX*, *AQP5* and *ESRRB* have the most promising evidence based on multiple replications and data supporting a functional role of these genes on caries (Table 6). Only one of the reviewed studies investigated associations with both periodontitis and caries (Ozturk et al. 2010). Cross-checking genes identified in the "periodontitis" search and genes identified in the "caries" search, no overlapping genes or SNPs were detected as associated with both diseases. Some genes (e.g. *DEFB1* gene and HLA locus) were shown to have weak associations with both diseases, and may need further research to clarify their potential role on both caries and periodontitis.

Tooth loss is a phenotype that in theory would measure the impact of both diseases in a population. Genetic variants for *IL1-alpha* and *IL1-beta* have been suggested as potential markers to identify individuals that may have higher risk for tooth loss (Giannobile et al. 2013, Vieira et al. 2015a,b). By extension, this genomic assessment could help determine which individuals could visit the dentist less often since they had decreased risk of tooth loss and would not benefit from additional preventive visits (Giannobile et al. 2013). This suggestion has been refuted by later analyses (Diehl et al. 2015). However, these analyses were not designed to test for gene-environmental interactions.

Hence, genomic data might still be useful if used in combination with other risk factors (i.e. diabetes, cardiovascular diseases and smoking; Vieira et al. 2015a,b). Despite some overlap between these two diseases when it relates to genetic contributions, not complete overlap can be expected, since different pathogenic pathways clearly exist. One example of a distinct mechanism affecting caries but likely not periodontitis is the exposure to fluorides. Although fluorides have some antimicrobial effects, which in theory could impact both diseases, the most relevant effect of fluorides is slowing the demineralization process, which impacts the overall caries experience of the population. The first experiments attempting to correlate the presence of genetic variants and the

ability of fluoride uptake by enamel did not show clear results (Shimizu et al. 2012).

Overall, this systematic review did not identify any genetic variant clearly associated with both caries and periodontitis. However, this could also be due to the limitations of how these diseases are defined and how inconsistently powered studies in general are. In particular, the authors believe that the disease caries needs to be defined beyond being present or absent and the number of past and present lesions or restorations. A suggestion is defining the disease based on multiple assessments done over time to create a "longitudinal pattern" of disease presentation that may be more meaningful and relate more directly to genetic risks.

Both caries and periodontitis are bacterially initiated diseases, so some of the same genes that regulate immune response could modulate susceptibility to both diseases. *LTF* is an example of potential antagonistic pleiotropy, suggested to be protective for caries but predisposing to localised aggressive periodontitis through an influence on biolfim composition (Fine 2015). Another area of interest that has not been studied is behaviour, which has a very important role on these diseases. The most studied genetically determined phenotype that may impact behaviours affecting caries is the ability to taste. Genes coding for the recognition of bitter, sweet and umami tastes have been defined (Bachmanov & Beauchamp 2007). As expected, preliminary work suggests that associations between these genes and caries exist (reviewed in Vieira et al. 2014). It is unlikely, however, that these data will provide new tools for managing dental caries, as it is well established that a diet rich in sugars that goes without proper oral hygiene will increase individual risks for the disease. Genes involved in our decision-making are emerging targets for research. Decision-making is a complex executive function, and choices are often made in dynamic situations that require evaluation of potential risk and reward. Decisions related to what and when to eat, perform oral hygiene activities and seek oral health care impact not only individual oral health but also the oral health of children. An inverted U-shaped relationship between dopaminergic function and cognitive performance exists, perhaps depending on the variation in optimal dopamine levels in relevant brain regions. This relationship is likely impacted by sex and genetic variation (Kohno et al. 2015). Understanding the biological process that leads to an individual decision for delaying oral hygiene, eating certain foods or avoiding professional oral health care and how that interacts with socioeconomic status, cultural believes, sex, age and geographical origin will provide a roadmap for dissecting the complexity of both caries and periodontitis aetiology. Although these diseases are highly preventable and their pathogenesis is quite well understood, the challenge of decreasing caries and periodontitis prevalence continues. The biology underlying individual oral health behaviours can lead to new insight on how to control disease in individuals at very high risk, the ultimate goal of current public health strategies (Vieira 2016).

An emerging line of investigation requiring more studies in caries and periodontitis is epigenetics, or the study of changes in organisms caused by modification of gene expression rather than alteration of the DNA sequence itself. Each tissue has a unique epigenetic profile, and changes can occur due to intrinsic (developmental, regenerative) and extrinsic (stress) factors (Lindroth & Park 2013). One of the best-documented epigenetic changes related to stress comes from the evaluation of cohorts from the Swedish Overkalix parish born in 1890, 1905 and 1920 until their death. The parents' or grandparents' access to food during the three cohorts slow growth period during childhood was determined. If food was not readily available due to failed harvests during the father's slow growth period, then cardiovascular disease mortality of their children was low. Conversely, diabetes mortality increased if the paternal grandfather was exposed to a surfeit of food during his slow growth period (Kaati et al. 2002). The pathogenesis of caries and periodontitis indeed involve regenerative bursts, both physiological in origin, as well as the result of treatments, and one can just assume these will influence future disease and should be somehow measured and considered.

Overall, this review presented an updated evidence of genetic variants associated with caries and periodontitis. Despite some potential common genetic pathways, no genetic variants have clearly been associated with both diseases to date. However, owing to the fast-evolving evidence on genetic associations, this work should be repeated periodically when more studies attempting to unveil the mechanisms underlying genetic associations have been produced. We also believe there is a need for developing better ways to measure and determine caries and periodontal disease and epigenetic changes. We do believe there is the potential that genomic approaches will be useful in the future for determining risk, management treatment and recall visits for our patients, but these likely need to be coupled with approaches that will be used for management of individuals at risk for other conditions as well such as asthma, diabetes, cancer and cardiovascular diseases.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. PRISMA checklist.
Appendix S2. Summary of search strategy.
Appendix S3. Modified AMSTAR score items.
Appendix S4. "Summary of evidence" table for the identification of genes and SNPs associated with presence of periodontitis.
Appendix S5. Modified AMSTAR quality score of systematic reviews included in the present review.
Appendix S6. Risk of bias of the included GWAS and candidate gene studies assessed through sensitivity analysis as previously described (Nibali 2013).

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Clinical Relevance

Scientific rationale for the study: Genetic variants are thought to influence the clinical manifestations of periodontal disease and caries, although evidence is still weak.

Principal findings: Evidence points towards a role for genetic variants affecting the host response in predisposing to periodontitis and caries. However, no clear shared genetic predisposing factors have emerged to date.

Practical implications: Further research is needed to identify whether genetic variants could predispose to both periodontal disease and caries.