HHS Public Access

Author manuscript

Adv Exp Med Biol. Author manuscript; available in PMC 2020 July 01.

Published in final edited form as:

Adv Exp Med Biol. 2019 ; 1197: 179–189. doi:10.1007/978-3-030-28524-1_13.

BIOLOGICALLY DEFINED OR BIOLOGICALLY INFORMED TRAITS ARE MORE HERITABLE THAN CLINICALLY DEFINED ONES: THE CASE OF ORAL AND DENTAL PHENOTYPES

Cary S. Agler[1], **Kevin Moss**[1], **Kamaira Philips**[1], **Julie T. Marchesan**[2], **Miguel Simancas-Pallares**[1], **James D. Beck**[2], **Kimon Divaris**[3,4]

[1]University of North Carolina-Chapel Hill, Adams School of Dentistry, Division of Oral and Craniofacial Health Sciences, Chapel Hill, NC, USA

[2]University of North Carolina-Chapel Hill, Adams School of Dentistry, Division of Comprehensive Oral Health Sciences, Chapel Hill, NC, USA

[3]University of North Carolina-Chapel Hill, Adams School of Dentistry, Division of Pediatrics and Public Health, Chapel Hill, NC, USA

[4]University of North Carolina-Chapel Hill, Gillings School of Global Public Health, Department of Epidemiology, Chapel Hill, NC, USA

Abstract

The genetic basis of oral health has long been theorized but little information exists on the heritable variance in common oral and dental disease traits explained by the human genome. We sought to add to the evidence base of heritability of oral and dental traits using high-density genotype data in a well-characterized community-based cohort of middle-age adults. We used genome-wide association (GWAS) data super-imposed to clinical and biomarker information generated in the context of the Dental Atherosclerosis Risk In Communities (ARIC) cohort. Genotypes comprised SNPs directly typed on the Affymetrix Genome-Wide Human SNP Array 6.0 chip with minor allele frequency of >5% (n=656,292) or imputed using HapMap II-CEU (n=2,104,905). We investigated 30 traits including 'global' [e.g., number of natural teeth (NT) and incident tooth loss], clinically defined (e.g., dental caries via the DMFS index, periodontitis via the CDC/AAP and WW17 classifications), and biologically informed ones (e.g., subgingival pathogen colonization and 'complex' traits). Heritability (i.e., variance explained; h^2) was calculated using Visscher's Genome-wide Complex Trait Analysis (GCTA) approach, using a random-effects mixed linear model and restricted maximum likelihood (REML) regression adjusting for ancestry (10 principal components), age and sex. H^2 estimates were modest for clinical traits—NT=0.11 (se=0.07), severe chronic periodontitis (CDC/AAP)=0.22 (se=0.19), WW17 Stage 4 vs. 1/2=0.15 (se=0.11). "Severe gingival index" and "high red complex colonization" had h^2>0.50, while a periodontal complex trait defined by high IL-1β GCF expression and *Aggregatibacter actinomycetemcomitans* subgingival colonization had the highest h^2=0.72 (se=0.32). Our results indicate that all GWAS SNPs explain modest levels of the observed variance in clinical oral and dental measures. Subgingival bacterial colonization and complex phenotypes encompassing both bacterial colonization and local inflammatory response had the highest heritability, suggesting that these biologically informed traits are promising targets for the conduct of genomics investigations, according to the notion of precision oral health.

Introduction

Most people worldwide are affected by common oral diseases and impairments—periodontitis, dental caries and tooth loss persist as clinical and public health problems (Frencken et al. 2017). Traditional oral health promotion approaches, relying on individual behavior change and dental office-based modalities have been generally unsuccessful in preventing the onset of oral disease and reducing health disparities (Kay, Locker 1996; Watt 2007). Emphasis on addressing risk factors that are shared with other health conditions, such smoking and cardiometabolic diseases, is a logical and efficient approach to improve the oral health of large segments of the population (Sheiham, Watt 2000). However, population-level risk factors and public health approaches, while optimal on average, may not be suitable for guiding the care of individuals (Rockhill 2001; Rose 2001). The advent of precision health care is expected to ameliorate this issue by accelerating the development and application of optimal care according to individuals' susceptibilities, lifestyles and environment (Collins, Varmus 2015).

The surge of scientific, biological and technological advances during last two decades has created promise and expectation that better preventive and therapeutic solutions are possible in dentistry. The development of precision health is based upon the premise that the current classification of people into diagnostic, susceptibility and treatment taxonomies can be improved (Divaris 2017). Traditional symptoms-based and clinically-defined categories are certainly foundational and valuable in healthcare—nevertheless, refined health and disease traits that are informed by the underlying biology are more likely to be "precise" (Chen, Snyder 2013). Examples of biologically informed research strategies have emerged in several domains of health care including, among others, cardiovascular disease (Leopold, Loscalzo 2018), neurology and psychiatry (Gibbs et al. 2018) and asthma care (Chung, Adcock 2019). Clinical or biological, phenotypic homogeneity is desirable for the development of optimal diagnostic, risk assessment and disease management applications and is likely better suited for interrogations of molecular context of health and disease (Robinson 2012; Divaris 2019a).

Above and beyond the necessary development of better disease taxonomies, comprehensive knowledge of individual susceptibility and factors that influence it are key elements for precision health. Environmental influences and genomics considered as the major determinants of disease susceptibility (Belsky et al. 2009; Rutter 2007). In the oral health domain, the genomics evidence base is growing but remains insufficient to inform care for the common, non-syndromic forms of periodontitis and dental caries (Divaris 2019b). This is in contrast with early and consistent observations that considerable variation in oral disease is attributable to heritable factors (Morelli et al. 2019). The genetic basis of oral health has long been theorized but little evidence exists on specific genetic factors underlying common oral and dental disease traits. For example, most reports of the heritability of periodontitis indicate that up to a third of the population variance of periodontitis is due to genetic factors, with more severe disease forms being more strongly genetically controlled (Nibali et al. 2019). Despite this evident heritability, the number of

consensus genes linked to periodontitis is less than a handful (Morelli et al. 2019; Shungin et al. 2019).

The advent of high-throughput genotyping and genome-wide association studies (GWAS) have helped the generation of massive phenotype-genotype association data (Buniello et al. 2019). This genomic information can be used to efficiently screen various phenotypes for "heritable content" (Zaitlen, Kraft 2012; Manolio et al. 2009) and aid inferences regarding disease sub-types that may be more genetically driven than others. In this paper, we report the results of a systematic examination of the heritable variance in 30 oral and dental traits explained by high-density genotypes generated in a GWAS among over 4,000 middle-age European American adults. The premise of this investigation is that oral and dental traits with high heritability are more likely to be biologically (versus environmentally) driven and may be optimal candidates for formal interrogations of genomic context and precision health applications.

Methods

The individuals used for all estimations of heritability were Americans of European descent, ages 53–74 years, participants of the Atherosclerosis Risk in Communities (ARIC) study (The ARIC Investigators 1989). This prospective cohort study was designed to examine cardiovascular disease risk using individuals living in four communities: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland. An ancillary dental study (dental ARIC) in which a comprehensive oral, periodontal and dental exam [including enumeration of missing teeth, probing pocket depth (PD), gingival recession, clinical attachment loss (CAL), etc.] was performed between 1996 and 1998 during the 4^{th} visit of the ARIC study (Beck et al. 2001). The visit also included an examination for dental caries experience and the collection of gingival crevicular fluid (GCF), as well as subgingival microbial plaque samples in a subset of participants. DNA was extracted from blood samples acquired during the study visit and genotyping was subsequently performed using the Genome-Wide Human SNP array 6.0 by Affymetrix containing 906,600 genetic markers (single nucleotide polymorphisms, SNPs). Additional SNPs were imputed using HapMap Phase II CEU build 36. Quality control procedures and criteria for all genotyping and imputation steps, analytical approaches including specific methods and software pipelines for the GWAS have been reported previously (Divaris et al. 2012; Divaris et al. 2013; Agler et al. 2009).

The clinical information, a follow-up telephone survey, and the collected biospecimens from the dental component of ARIC has been used to generate several oral/dental phenotypes. For the purposes of this study we examined the following trait domains: number of remaining natural teeth at the baseline examination, incident tooth loss [>2 teeth over a 10-year period, assessed via a telephone survey; (Naorungroj et al. 2017)]; dental caries [DMFS index; (Wang et al. 2012) and tooth morbidity, DM_TFS index (Morelli et al. 2019; Shungin et al. 2019)]; periodontitis [defined using the CDC/AAP chronic periodontitis definition (Page, Eke 2013); the 2017 world workshop classification (WW17; Papapanou et al. 2018); extent probing depth and attachment loss scores (Carlos et al. 1986); mean interproximal attachment loss (Sanders et al. 2017)]; periodontal profile classes (PPC; Morelli et al. 2017;

Morelli et al. 2018); subgingival pathogen colonization (Divaris et al. 2012); gingival crevicular fluid (GCF) interleukin(IL)-1β expression (Offenbacher et al. 2018); and periodontal complex traits (PCT) (Offenbacher et al. 2016). The PPC classification (Morelli et al. 2017) entails an empirically derived 7-category taxonomy that accounts for intra-oral patterns of tooth loss whereas the 6 PCTs (Offenbacher et al. 2016) are essentially vectors of "biological variance" [i.e., subgingival colonization patterns and host inflammatory response (GCF IL-1β), combined with clinical parameters] in periodontitis. Of note, WW17 Stages 3 and 4, both having interdental CAL≥5mm, were differentiated in the ARIC dataset based on the existence of tooth loss due to periodontitis (≥5 teeth) or <20 remaining teeth (i.e., 10 opposing pairs).

The heritable variance (h^2) in these traits that could be attributable to the human genome was estimated using Visscher's genome-wide complex trait analysis (GCTA) (Yang et al. 2011; Yang et al. 2013). The GCTA approach allows the estimation of heritability using the common SNPs available on most genotyping arrays and unrelated individuals (the same data used to perform most GWAS). This is done by, first, estimation of a genetic relationship matrix (GRM) using all genotyped individuals. In a second step, the GRM is carried forward to restricted maximum likelihood (REML) analysis to obtain the proportion of trait variance explained by all the SNPs. The estimated variance explained may be influenced by the unknown linkage disequilibrium (LD) structure of all GWAS SNPs with causal variants—which is generally unknown or unobservable. Therefore, we used two different sets of SNPs for the computation of the GRM: all genotyped SNPs (n=656,292; considered to be the highest quality SNP set) and all genotyped and imputed SNPs with imputation quality score (R^2)≥0.6 (n=2,104,905; considered to be the most inclusive SNP set). SNPs with minor allele frequency (MAF) less than 5% were excluded from the creation of both GRMs. We computed and report h^2 and standard errors (se) for both SNP sets, as well as using crude [i.e., considering only ancestry, adjusted using 10 population stratification principal components (PC; Price et al. 2016)] and adjusted genetic models [i.e., including terms for 10 PCs, as well as age (in years) and sex (binary)].

Results

Heritability estimates for the 'traditional', clinically defined oral and dental traits are presented in Table 1. Considering the high-quality set of SNPs and adjusted models, severe chronic periodontitis was the periodontal trait with the highest h^2 (0.22), followed by extent probing depth ≥4mm and mean interproximal attachment loss (0.19 and 0.15, respectively). The tooth morbidity index (i.e., DM_TFS is the traditional DMFS with the addition of teeth/surfaces lost due to all causes) showed almost double the heritability of the dental caries experience DMFS index (0.24 versus 0.13). Of note, comparison of crude versus adjusted (i.e., including age and sex) model did not reveal any substantial differences, whereas directly genotyped SNP sets generally resulted in higher h^2 estimates compared to those obtained by the larger set including both genotyped and imputed SNPs.

Results of heritability estimation for PPC and WW17 derived contrasts, representing two 'contemporary' clinical classification systems, are presented in Table 2. With regards to the WW17 classification, our sample included a very small number of participants classified as

Stage 1, therefore we treated Stages 1 and 2 as one group and contrasted it with combinations of participants in Stages 3 and 4. Stage 4 versus Stage 1 and 2 was the contrast producing the highest h^2 estimate, essentially double than what was obtained for Stage 3 (0.15 versus 0.08). When considering the PPC classification, we examined 7 contrasts, i.e., various disease categories versus health. The "gigh gingival index" (PPC-C, as presented in Morelli et al. 2016) produced by far the highest heritability: h^2=0.52 (se=0.19), followed by "severe disease" [PPC-G; h^2=0.26 (se=0.19)] and "severe disease" or "severe tooth loss" [PPC-F; h^2=0.26 (se=0.15)].

The estimates of phenotypic variance explained in the biologically defined (i.e., subgingival pathogen colonization and GCF IL-1β expression) and biologically informed (i.e., PCTs) are presented in Table 3. Both microbial traits showed high heritability, with the red complex demonstrating h^2=0.53 (se=0.31) and the orange complex demonstrating h^2=0.46 (se=0.32). High (top quartile) GCF IL-1β showed only modest heritability, of 0.16. With regards to PCTs, the heritability of 2 complex traits (PCT-1 and PCT-4) was estimated as near zero. In contrast, PCT-3 (the "*A. actinomycetemcomitans* trait" according to Offenbacher et al. 2016) showed the highest heritability estimate in our analysis, h^2=0.72 (se=0.32), followed by PCT-6, h^2=0.40 (se=0.35).

Discussion

In this paper we present the results of a comprehensive exploration of the heritability of 30 oral and dental traits, as approximated by phenotypic variance explained by a two large sets of GWAS SNPs, among a sizeable sample of middle-aged European Americans. Our results indicate substantially higher variance explained by the genome for biologically defined and biologically informed traits compared to clinically defined ones. Importantly, traits representing high levels of inflammation and severe disease (i.e., "severe periodontitis, "severe tooth loss", "high red complex colonization" of bacterial colonization criteria) traits were, the ones encompassing most genetic (i.e., heritable) signal. These results are in support of our thesis regarding the suitability of homogeneous and biologically informed oral and dental traits for genetic investigations and, downstream, precision health applications.

A plausible interpretation of our findings revolves around the notion of "endophenotypes" (Ghiassian et al. 2016)—biological intermediates of clinical disease (e.g., serum lipids in the context of cardiovascular disease), typically considered as biological vectors underlying a proportion of cases. Because these traits are closer to biological and physiological parameters reflecting the disease process, their genomics interrogation may be both fruitful (i.e., a genetic association signal may be easier to detect versus for a heterogeneous clinical outcome) and impactful—genetic discoveries for biological disease intermediates may provide clues for 'druggable' pathways or other mechanistic interventions (Ramanan, Saykin 2013). Our finding of the highest heritability for PCT-3, a composite trait including an aggressive periodontal pathogen (*A. actinomycetemcomitans*), the local inflammatory host response (GCF IL-1β), combined with high levels of clinically manifested disease, is unsurprising (Lopez et al. 2015). Similarly, our finding of over 50% heritability for the "high gingival index" trait points to a possibly latent hyper-inflammatory trait that may be

expressed above and beyond clinical attachment loss and tooth loss. In fact, our group was reported an association between the *ASIC2* locus (Zhang et al. 2016) and severe gingival inflammation.

Our findings of near zero variance explained by the genome for PCT-1 and PCT-4 do not imply that heritability for these traits is exactly zero, as GCTA typically captures the lower bound of heritability; however, we would argue that, based on these findings, heritability for these traits should be much less than what we found for the other PCTs. We must acknowledge that, despite this low estimated heritability, our group has identified and followed-up several genome-wide significant loci for PCT-1, including *IFI16* and *AIM2* (Marchesan et al. 2017), as well as for PCT-4 using gene-centric analyses (Offenbacher et al. 2016; Rhodin et al. 2014). Moreover, PCT-6 has the interesting feature of being the only PCT significantly associated with sex, age, smoking and diabetes (Offenbacher et al. 2016), which are known important risk factors for periodontitis.

It is important to acknowledge that there is ongoing dialogue regarding the merits and limitations of the GCTA method (Krishna Kumar et al. 2016; Yang et al. 2016). The method has been used extensively for the interrogation of several traits, producing results that have been validated both empirically and mathematically (Lee, Chow 2014). In general, we consider that GCTA computes that lowest bound of true heritability under common assumptions for common-complex diseases and traits (Lee, Chow 2014), because it typically disregards low-frequency variants, variants' postulated causal or functional roles, as well as any interactions that may be part of the so-called "missing heritability" (Manolio et al. 2009). Of note, in a previous study (Divaris et al. 2013), we found that the inclusion of a genome-wide interaction with smoking (treated as a binary variable; ever/never) in the genetic model increased the explained variance in severe chronic periodontitis to over 50%. It is likely and to some degree expected that different heritability estimates might be obtained in a different population with different age distribution, ancestral background, environmental or behavioral risk factors, disease prevalence, etc. However, in this paper, we consider h^2 estimates relative to each other and not in absolute terms.

In sum, our results indicate that genome-wide sets of polymorphisms explain modest levels of the observed variance in clinical oral and dental measures, those traditionally used to define and classify disease. Subgingival bacterial colonization and complex phenotypes that encompass both bacterial colonization and local inflammatory response had the highest heritability, suggesting that these biologically informed traits are promising targets for the conduct of genomics investigations, because they arguably contain most genetic signal and are more homogeneous than clinically defined disease taxonomies. These features are highly desirable for developing precision health solutions because they enable the re-classification of individuals to more homogeneous health and disease groups with the hopes of optimizing prevention, diagnosis and therapy (Insel, Cuthbert 2015). Based on our findings, we posit that new, further enriched biological phenotypes (i.e., based upon additional data on microbial colonization, as well as biomarker mediators and effector molecular pathways) can be used to define new disease subtypes and enable us to better understand the molecular basis of oral diseases, thereby facilitating the development of precision prevention and therapies.

Acknowledgements

Drs. Divaris and Agler are supported by a grant from the National Institutes of Health/National Institute of Dental and Craniofacial Health Research (NIH/NIDCR) U01-DE025046. Dr. Marchesan is supported by K01-DE027087.

References

Agler CS, Shungin D, Ferreira Zandoná AG, Schmadeke P, Basta PV, Luo J et al. Protocols, Methods, and Tools for Genome-Wide Association Studies (GWAS) of Dental Traits. Methods Mol Biol. 2019;1922:493–509. doi:10.1007/978-1-4939-9012-2_38. [PubMed: 30838596]

Beck JD, Elter JR, Heiss G, Couper D, Mauriello SM, Offenbacher S. Relationship of periodontal disease to carotid artery intima-media wall thickness: the atherosclerosis risk in communities (ARIC) study. Arterioscler Thromb Vasc Biol. 2001;21(11):1816–22. [PubMed: 11701471]

Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? Mol Psychiatry. 2009;14(8):746–54. doi: 10.1038/mp.2009.44. [PubMed: 19455150]

Buniello A, MacArthur JAL, Cerezo M, Harris LW, Hayhurst J, Malangone C et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. Nucleic Acids Res. 2019;47(D1):D1005–D12. doi: 10.1093/nar/gky1120. [PubMed: 30445434]

Carlos JP, Wolfe MD, Kingman A. The extent and severity index: a simple method for use in epidemiologic studies of periodontal disease. J Clin Periodontol. 1986;13(5):500–5. [PubMed: 3459740]

Chen R, Snyder M. Promise of personalized omics to precision medicine. Wiley Interdiscip Rev Syst Biol Med. 2013;5(1):73–82. doi: 10.1002/wsbm.1198. [PubMed: 23184638]

Chung KF, Adcock IM. Precision Medicine for the discovery of treatable mechanisms in severe asthma. Allergy. 2019 3 13. doi: 10.1111/all.13771.

Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372(9):793–5. doi: 10.1056/NEJMp1500523. [PubMed: 25635347]

Divaris K, Monda KL, North KE, Olshan AF, Lange EM, Moss K et al. Genome-wide association study of periodontal pathogen colonization. J Dent Res. 2012;91(7 Suppl):21S–8S. [PubMed: 22699663]

Divaris K, Monda KL, North KE, Olshan AF, Reynolds LM, Hsueh WC et al. Exploring the genetic basis of chronic periodontitis: a genome-wide association study. Hum Mol Genet. 2013;22(11):2312–24. doi: 10.1093/hmg/ddt065. [PubMed: 23459936]

Divaris K Fundamentals of Precision Medicine. Compend Contin Educ Dent. 2017;38(8 Suppl):30–2. [PubMed: 29227115]

Divaris K Searching deep and wide: advances in the molecular understanding of dental caries and periodontal disease. Adv Dent Res. 2019a In Press

Divaris K The era of the genome and dental medicine. J Dent Res. 2019b In Press

Frencken JE, Sharma P, Stenhouse L, Green D, Laverty D, Dietrich T. Global epidemiology of dental caries and severe periodontitis - a comprehensive review. J Clin Periodontol. 2017;44 Suppl 18:S94–S105. doi: 10.1111/jcpe.12677. [PubMed: 28266116]

Ghiassian SD, Menche J, Chasman DI, Giulianini F, Wang R, Ricchiuto P et al. Endophenotype Network Models: Common Core of Complex Diseases. Sci Rep. 2016;6:27414. doi: 10.1038/srep27414. [PubMed: 27278246]

Gibbs RM, Lipnick S, Bateman JW, Chen L, Cousins HC, Hubbard EG et al. Toward Precision Medicine for Neurological and Neuropsychiatric Disorders. Cell Stem Cell. 2018;23(1):21–4. doi: 10.1016/j.stem.2018.05.019. [PubMed: 29887317]

Insel TR, Cuthbert BN. Medicine. Brain disorders? Precisely. Science. 2015;348(6234):499–500. doi: 10.1126/science.aab2358. [PubMed: 25931539]

Kay EJ, Locker D. Is dental health education effective? A systematic review of current evidence. Community Dent Oral Epidemiol. 1996;24(4):231–5. [PubMed: 8871028]

Krishna Kumar S, Feldman MW, Rehkopf DH, Tuljapurkar S. Limitations of GCTA as a solution to the missing heritability problem. Proc Natl Acad Sci U S A. 2016;113(1):E61–70. doi: 10.1073/pnas.1520109113. [PubMed: 26699465]

Lee JJ, Chow CC. Conditions for the validity of SNP-based heritability estimation. Hum Genet. 2014;133(8):1011–22. doi: 10.1007/s00439-014-1441-5. [PubMed: 24744256]

Leopold JA, Loscalzo J. Emerging Role of Precision Medicine in Cardiovascular Disease. Circ Res. 2018;122(9):1302–15. doi: 10.1161/CIRCRESAHA.117.310782. [PubMed: 29700074]

Lopez R, Hujoel P, Belibasakis GN. On putative periodontal pathogens: an epidemiological perspective. Virulence. 2015;6(3):249–57. doi: 10.1080/21505594.2015.1014266. [PubMed: 25874553]

Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ et al. Finding the missing heritability of complex diseases. Nature. 2009;461(7265):747–53. doi: 10.1038/nature08494. [PubMed: 19812666]

Marchesan JT, Jiao Y, Moss K, Divaris K, Seaman W, Webster-Cyriaque J et al. Common polymorphisms in IFI16 and AIM2 genes are associated with periodontal disease. J Periodontol. 2017;88(7):663–72. doi: 10.1902/jop.2017.160553. [PubMed: 28387608]

Morelli T, Agler CS, Divaris K. Genomics of periodontal disease and tooth morbidity. Periodontol 2000. 2019 In Press

Morelli T, Moss KL, Beck J, Preisser JS, Wu D, Divaris K et al. Derivation and validation of the Periodontal and Tooth Profile Classification System for patient stratification. J Periodontol. 2017;88(2):153–65. [PubMed: 27620653]

Morelli T, Moss KL, Preisser JS, Beck JD, Divaris K, Wu D et al. Periodontal profile classes predict periodontal disease progression and tooth loss. J Periodontol. 2018;89(2):148–56. doi: 10.1002/JPER.17-0427. [PubMed: 29520822]

Naorungroj S, Slade GD, Divaris K, Heiss G, Offenbacher S, Beck JD. Racial differences in periodontal disease and 10-year self-reported tooth loss among late middle-aged and older adults: the dental ARIC study. J Public Health Dent. 2017;77(4):372–82. doi: 10.1111/jphd.12226. [PubMed: 28585323]

Nibali L, Bayliss-Chapman J, Almofareh SA, Zhou Y, Divaris K, Vieira AR. What is the heritability of periodontal disease? A systematic review. J Dent Res. 2019;98(6):632–41. [PubMed: 31107142]

Offenbacher S, Divaris K, Barros SP, Moss KL, Marchesan JT, Morelli T et al. Genome-wide association study of biologically informed periodontal complex traits offers novel insights into the genetic basis of periodontal disease. Hum Mol Genet. 2016;25(10):2113–29. [PubMed: 26962152]

Offenbacher S, Jiao Y, Kim SJ, Marchesan J, Moss KL, Jing L et al. GWAS for Interleukin-1β levels in gingival crevicular fluid identifies IL37 variants in periodontal inflammation. Nat Commun. 2018;9(1):3686. doi: 10.1038/s41467-018-05940-9. [PubMed: 30206230]

Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. J Periodontol. 2007;78(7 Suppl):1387–99.

Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018;89 Suppl 1:S173–S82. doi: 10.1002/JPER.17-0721. [PubMed: 29926951]

Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet. 2006;38(8):904–9. [PubMed: 16862161]

Ramanan VK, Saykin AJ. Pathways to neurodegeneration: mechanistic insights from GWAS in Alzheimer's disease, Parkinson's disease, and related disorders. Am J Neurodegener Dis. 2013;2(3):145–75. [PubMed: 24093081]

Rhodin K, Divaris K, North KE, Barros SP, Moss K, Beck JD et al. Chronic periodontitis genome-wide association studies: gene-centric and gene set enrichment analyses. J Dent Res. 2014;93(9):882–90. doi: 10.1177/0022034514544506. [PubMed: 25056994]

Robinson PN. Deep phenotyping for precision medicine. Hum Mutat. 2012;33(5):777–80. doi: 10.1002/humu.22080. [PubMed: 22504886]

Rockhill B The privatization of risk. Am J Public Health. 2001;91(3):365–8. [PubMed: 11236399]

Rose G Sick individuals and sick populations. Int J Epidemiol. 2001;30(3):427–32. [PubMed: 11416056]

Rutter M Gene-environment interdependence. Dev Sci. 2007;10(1):12–8. [PubMed: 17181693]

Sanders AE, Wong Q, Sofer T, Agler C, Shaffer JR, Beck JD et al. Genome-Wide Association Study of Chronic Periodontitis in the Hispanic/Latino Community: HCHS/SOL. J Dent Res 2017;96(1):64–72. [PubMed: 27601451]

Sheiham A, Watt RG. The common risk factor approach: a rational basis for promoting oral health. Community Dent Oral Epidemiol. 2000;28(6):399–406. [PubMed: 11106011]

Shungin D, Haworth S, Divaris K, Agler CS, Kamatani Y, Keun Lee M et al. Genome-wide analysis of dental caries and periodontitis combining clinical and self-reported data. Nat Commun. 2019;10(1):2773. doi: 10.1038/s41467-019-10630-1. [PubMed: 31235808]

The ARIC investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol. 1989;129(4):687–702. [PubMed: 2646917]

Wang X, Shaffer JR, Zeng Z, Begum F, Vieira AR, Noel J et al. Genome-wide association scan of dental caries in the permanent dentition. BMC Oral Health. 2012;12:57. doi: 10.1186/1472-6831-12-57. [PubMed: 23259602]

Watt RG. From victim blaming to upstream action: tackling the social determinants of oral health inequalities. Community Dent Oral Epidemiol. 2007;35(1):1–11. [PubMed: 17244132]

Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. Am J Hum Genet. 2011;88(1):76–82. doi: 10.1016/j.ajhg.2010.11.011. [PubMed: 21167468]

Yang J, Lee SH, Goddard ME, Visscher PM. Genome-wide complex trait analysis (GCTA): methods, data analyses, and interpretations. Methods Mol Biol. 2013;1019:215–36. doi: 10.1007/978-1-62703-447-0_9. [PubMed: 23756893]

Yang J, Lee SH, Wray NR, Goddard ME, Visscher PM. GCTA-GREML accounts for linkage disequilibrium when estimating genetic variance from genome-wide SNPs. Proc Natl Acad Sci U S A. 2016;113(32):E4579–80. doi: 10.1073/pnas.1602743113. [PubMed: 27457963]

Zaitlen N, Kraft P. Heritability in the genome-wide association era. Hum Genet. 2012;131(10):1655–64. doi: 10.1007/s00439-012-1199-6. [PubMed: 22821350]

Zhang S, Divaris K, Moss K, Yu N, Barros S, Marchesan J et al. The Novel ASIC2 Locus is associated with severe gingival inflammation. JDR Clin Trans Res. 2016;1(2):163–70. doi: 10.1177/2380084416645290. [PubMed: 28459102]

Table 1.

Phenotypic variance explained for 'traditional', clinically-defined oral and dental traits by all genotyped and imputed autosomal SNPs available among the European American participants of the Dental Atherosclerosis Risk In Communities study (n = 4,504).

		Genotyped SNPs		**Imputed[a] SNPs**
Exclusion filters:		MAF < 0.05		MAF < 0.05, $R^{2(b)}$ < 0.6
n (SNPs)[c]:		656,292		2,104,905
		variance explained (se)		variance explained (se)
Number of remaining teeth				
+ 10 PCs for population structure		0.115 (0.07)		0.065 (0.06)
+ 10 PCs, sex, age		0.114 (0.07)		0.064 (0.06)
Incident Tooth Loss[d]				
+ 10 PCs for population structure		0.064 (0.11)		0.006 (0.09)
+ 10 PCs, sex, age		0.055 (0.11)		0.001 (0.10)
DMFS (decayed, missing, filled tooth surfaces due to caries)				
+ 10 PCs for population structure		0.126 (0.08)		0.057 (0.06)
+ 10 PCs, sex, age		0.131 (0.08)		0.066 (0.06)
Tooth morbidity (DMFS including teeth lost due to all causes)				
+ 10 PCs for population structure		0.256 (0.07)		0.184 (0.06)
+ 10 PCs, sex, age		0.242 (0.07)		0.171 (0.06)
Any periodontitis (moderate/severe versus health/mild)				
+ 10 PCs for population structure		0.012 (0.07)		0.039 (0.06)
+ 10 PCs, sex, age		0.018 (0.08)		0.049 (0.06)
Moderate periodontitis (versus health/mild)				
+ 10 PCs for population structure		0.006 (0.14)		0.068 (0.12)
+ 10 PCs, sex, age		0.000 (0.14)		0.066 (0.12)
Severe periodontitis (versus health/mild)				
+ 10 PCs for population structure		0.175 (0.19)		0.083 (0.16)
+ 10 PCs, sex, age		0.220 (0.19)		0.127 (0.16)
Mean interproximal attachment loss				
+ 10 PCs for population structure		0.161 (0.07)		0.122 (0.06)
+ 10 PCs, sex, age		0.152 (0.08)		0.106 (0.06)
Extent of attachment loss ≥ 3mm (proportion of sites)				
+ 10 PCs for population structure		0.113 (0.08)		0.073 (0.06)
+ 10 PCs, sex, age		0.075 (0.08)		0.037 (0.06)
Extent of attachment loss ≥ 4mm (proportion of sites)				
+ 10 PCs for population structure		0.092 (0.07)		0.053 (0.06)
+ 10 PCs, sex, age		0.076 (0.07)		0.035 (0.06)

		Genotyped SNPs		Imputed[a] SNPs
Extent of probing depth ≥ 4mm (proportion of sites)				
+ 10 PCs for population structure		0.167 (0.07)		0.143 (0.06)
+ 10 PCs, sex, age		0.190 (0.07)		0.150 (0.06)

MAF, minor allele frequency; se, standard error; PCs, principal components

[a] Imputed using HapMap II-CEU

[b] Imputation quality score

[c] Number of SNPs that were used to estimate the genetic relationship matrix after exclusions, among the study participants as a first step in the GCTA prior to conducting REML

[d] Incident tooth loss was derived from a follow-up telephone survey in a subset of participants (n = 2,771) and defined as >2 teeth lost during the last decade

Table 2.

Phenotypic variance explained for contemporary classifications of periodontitis by all genotyped and imputed autosomal SNPs available among European American participants of the Dental Atherosclerosis Risk In Communities study.

		Genotyped SNPs		**Imputed[a] SNPs**
Exclusion filters:		MAF < 0.05		MAF < 0.05, $R^{2(b)}$ < 0.6
n (SNPs)[c]:	n	656,292		2,104,905
		variance explained (se)		variance explained (se)
any PPC[d] (disease) vs. healthy	4,504			
+ 10 PCs for population structure		0.084 (0.07)		0.064 (0.06)
+ 10 PCs, sex, age		0.073 (0.07)		0.056 (0.06)
PPC[d]: "high gingival index" vs. healthy	1,621			
+ 10 PCs for population structure		0.479 (0.19)		0.397 (0.17)
+ 10 PCs, sex, age		0.517 (0.19)		0.454 (0.17)
PPC[d]: "posterior disease", "severe disease", "tooth loss", "severe tooth loss" vs. healthy	3,532			
+ 10 PCs for population structure		0.041 (0.09)		0.046 (0.08)
+ 10 PCs, sex, age		0.038 (0.09)		0.047 (0.08)
PPC[d]: "posterior disease", "severe disease", "tooth loss", "severe tooth loss" vs. healthy	2,705			
+ 10 PCs for population structure		0.155 (0.12)		0.120 (0.10)
+ 10 PCs, sex, age		0.149 (0.12)		0.126 (0.10)
PPC[d]: "severe disease" vs. healthy	1,699			
+ 10 PCs for population structure		0.272 (0.19)		0.158 (0.17)
+ 10 PCs, sex, age		0.257 (0.19)		0.142 (0.17)
PPC[d]: "severe disease", "severe tooth loss" vs. healthy	2,174			
+ 10 PCs for population structure		0.245 (0.15)		0.152 (0.13)
+ 10 PCs, sex, age		0.261 (0.15)		0.171 (0.13)
PPC[d]: "tooth loss", "severe tooth loss" vs. healthy	2,467			
+ 10 PCs for population structure		0.103 (0.13)		0.079 (0.11)
+ 10 PCs, sex, age		0.106 (0.13)		0.096 (0.11)
Periodontitis WW17[e] Stage 3 vs. 1/2	3,414			
+ 10 PCs for population structure		0.062 (0.10)		0.108 (0.08)
+ 10 PCs, sex, age		0.076 (0.10)		0.123 (0.08)
Periodontitis WW17[e] Stage 3/4 vs. 1/2	3,047			
+ 10 PCs for population structure		0.079 (0.07)		0.103 (0.06)
+ 10 PCs, sex, age		0.084 (0.07)		0.116 (0.06)

		Genotyped SNPs		Imputed[a] SNPs
Periodontitis WW17[e] Stage 4 vs. 1/2	4,504			
+ 10 PCs for population structure		0.175 (0.11)		0.139 (0.09)
+ 10 PCs, sex, age		0.146 (0.11)		0.125 (0.09)

MAF, minor allele frequency; se, standard error; PCs, principal components

[a] Imputed using HapMap II-CEU

[b] Imputation quality score

[c] Number of SNPs that were used to estimate the genetic relationship matrix after exclusions, among the study participants as a first step in the GCTA prior to conducting REML

[d] Periodontal profile class, introduced by Morelli et al. 2016

[e] 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions (Papapanou et al. 2018)

Table 3.

Phenotypic variance explained for 2 bacterial colonization and 6 biologically informed complex periodontal traits (PCT) by all genotyped and imputed autosomal SNPs available, among European American participants of the Dental Atherosclerosis Risk In Communities study

		Genotyped SNPs		Imputed[a] SNPs
Exclusion filters:		MAF < 0.05		MAF < 0.05, $R^{2(b)}$ < 0.6
n (SNPs)[c]:	n	656,292		2,104,905
		variance explained (se)		variance explained (se)
High[d] orange complex colonization	978			
+ 10 PCs for population structure		0.464 (0.32)		0.318 (0.30)
+ 10 PCs, sex, age		0.456 (0.32)		0.310 (0.29)
High[d] red complex colonization	986			
+ 10 PCs for population structure		0.565 (0.31)		0.424 (0.29)
+ 10 PCs, sex, age		0.534 (0.31)		0.405 (0.29)
High[e] GCF IL-1β expression	4,907			
+ 10 PCs for population structure		0.156 (0.08)		0.155 (0.08)
+ 10 PCs, sex, age		0.155 (0.08)		0.156 (0.08)
PCT[f]1	975			
+ 10 PCs for population structure		<0.0001		<0.0001
+ 10 PCs, sex, age		<0.0001		<0.0001
PCT[f]2	975			
+ 10 PCs for population structure		0.18 (0.36)		0.01 (0.31)
+ 10 PCs, sex, age		0.14 (0.36)		<0.0001
PCT[f]3	975			
+ 10 PCs for population structure		0.71 (0.32)		0.57 (0.30)
+ 10 PCs, sex, age		0.72 (0.32)		0.57 (0.31)
PCT[f]4	975			
+ 10 PCs for population structure		<0.0001		<0.0001
+ 10 PCs, sex, age		<0.0001		<0.0001
PCT[f]5	975			
+ 10 PCs for population structure		0.16 (0.35)		0.15 (0.31)
+ 10 PCs, sex, age		0.18 (0.35)		0.17 (0.31)
PCT[f]6	975			
+ 10 PCs for population structure		0.19 (0.36)		0.19 (0.31)
+ 10 PCs, sex, age		0.40 (0.35)		0.35 (0.31)

MAF, minor allele frequency; se, standard error; PCs, principal components

[a] Imputed using HapMap II-CEU

[b] Imputation quality score

[c] Number of SNPs that were used to estimate the genetic relationship matrix after exclusions, among the study participants as a first step in the GCTA prior to conducting REML

[d] Defined as the highest quintile versus the lower 4 quintiles, as quantitated by checkerboard DNA-DNA hybridization (Divaris et al. 2012)

[e] Defined as the top quartile versus the lower 3 quartiles (Offenbacher et al. 2018)

[f] Periodontal complex trait, introduced by Offenbacher et al. 2016