



Genetic architecture of dental traits: mapping and pathway enrichment of genome-wide associations

Arquitectura genética de los rasgos dentales: mapeo y enriquecimiento de vías de asociaciones genómicas

Nairobi Hernández Bridon¹  

¹ Instituto de Investigaciones en Microbiología y Parasitología Médica. Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET). Universidad de Buenos Aires. Ciudad Autónoma de Buenos Aires, Argentina

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Corresponding Author: Nairobi Hernández Bridon 

ABSTRACT

Introduction: Genome-wide association studies have identified many loci for dental traits, but the mapped genes, biological pathways, and population diversity of this literature have not been characterized together. **Methods:** The NHGRI-EBI GWAS Catalog was queried for dental trait studies, associations were mapped to genes, gene ontology enrichment was performed with g:Profiler, and the ancestry composition of the studied cohorts was tabulated. **Results:** Sixty-six studies across five trait groups contributed 181,856 associations mapping to 13,563 genes. Periodontitis had the most associations (99,834) and genes (12,183), developmental and structural processes were the top enriched pathways, and 58.6% of studied cohorts were of European ancestry. **Conclusions:** The genetic architecture of dental traits is dominated by periodontitis and enamel and dentin structure, converges on developmental and structural pathways, and remains heavily European in its ancestry representation.

Keywords: dental traits; genome-wide association study; gene mapping; pathway enrichment; genetic ancestry.

RESUMEN

Introducción: Los estudios de asociación del genoma completo han identificado muchos loci para rasgos dentales, pero los genes mapeados, las vías biológicas y la diversidad poblacional de esta literatura no se han caracterizado en conjunto. **Métodos:** Se consultó el catálogo GWAS de NHGRI-EBI para estudios de rasgos dentales, se mapearon las asociaciones a genes, se realizó enriquecimiento de ontología génica con g:Profiler y se tabuló la composición de ascendencia de las cohortes estudiadas. **Resultados:** Sesenta y seis estudios en cinco grupos de rasgos aportaron 181 856 asociaciones que mapean a 13 563 genes. La periodontitis tuvo más asociaciones (99 834) y genes (12 183), los procesos de desarrollo y estructura fueron las vías más enriquecidas, y el 58,6 % de las cohortes estudiadas eran de ascendencia europea. **Conclusiones:** La arquitectura genética de los rasgos dentales está dominada por la periodontitis y la estructura del esmalte y la dentina, converge en vías de desarrollo y estructura, y sigue siendo mayoritariamente europea en su representación de ascendencia.

Palabras clave: rasgos dentales; estudio de asociación del genoma completo; mapeo de genes; enriquecimiento de vías; ascendencia genética.

INTRODUCTION

Genome-wide association studies have transformed the understanding of common dental traits by identifying reproducible genetic loci for caries, periodontitis, tooth agenesis, and tooth structure, yet the field has grown in a way that makes synthesis difficult, with each trait studied in a separate literature and few attempts to map them together.(1,2)

The earliest dental genome-wide association studies, conducted in the late 2000s and early 2010s, focused on caries and periodontitis in relatively small samples and yielded few replicable loci, but the subsequent decade brought large meta-analyses and whole-phenome studies that expanded the catalog of associated loci by orders of magnitude, and the field now spans the full range from common inflammatory traits to rare developmental phenotypes.

The mapped genes reported by these studies span developmental transcription factors such as PAX9 and MSX1, which are mutated in the Mendelian forms of tooth agenesis, structural enamel proteins such as amelogenin and enamelin, which are mutated in amelogenesis imperfecta, and immune regulators that predispose to periodontitis, and their biological interpretation depends on knowing which pathways they converge on, information that is scattered across individual reports rather than assembled in one place.(3,4)

The fact that the same genes recur in both rare Mendelian disorders and common complex traits is a well-known feature of dental genetics, and it means that a pathway-level synthesis of the common-variant literature can draw on the rich functional annotation that the Mendelian literature has accumulated.

The classic analyses of Shungin et al.(5) established that caries and periodontitis have partly shared and partly distinct genetic architectures, and the more recent whole-oral-disease analyses of Karppinen et al.(6) extended this to dozens of oral phenotypes, but a synthesis of the mapped genes and their pathways across the major dental trait groups has not been assembled.

The question of how diverse the studied populations are is equally pressing, because most genome-wide association studies have been conducted in European ancestry populations, and the extent to which dental trait genetics has repeated this pattern or departed from it has not been quantified.(7,8)

The epidemiology of dental disease is, if anything, the inverse of the ancestry distribution of its genetic studies, since caries and periodontitis burden is highest in low- and middle-income settings and in minority populations, which means that a genetic literature skewed toward European ancestry is least informative precisely for the populations that need it most.

This mismatch between where the disease is and where the genetics is done is not unique to dentistry, but it is particularly consequential for a field whose ultimate goal is prevention, because the genetic findings are only useful to the extent that they can be applied to the populations in which the disease burden is concentrated. A single analysis that maps the genes, pathways, and ancestry of dental trait genetics therefore serves both a scientific and an equity purpose, by showing what has been learned and for whom.

The value of a unified mapping lies in the questions it makes answerable. With a single corpus of dental trait associations, one can ask how the burden of associations and mapped genes is distributed across traits, which biological pathways the mapped genes converge on, and whether the ancestry composition of the studied cohorts reflects the global burden of dental disease.

Each of these questions has a practical consequence: the trait distribution tells funders where the genetic evidence is thin, the pathway convergence tells biologists where to look for mechanism, and the ancestry composition tells the field whether its polygenic tools will travel to the populations that need them.

Previous summaries have addressed individual traits, such as the systematic review of caries genome-wide association studies by Zhou,(9) the genetic reviews of tooth agenesis by Duke,(10) Modafferi,(11) and Fallea,(12) and the genomics of periodontal disease reviewed by Morelli,(13) but none has assembled the five major dental trait groups together with gene mapping, pathway enrichment, and ancestry in a single analysis.

The trait-specific reviews are valuable within their scope, but they cannot answer the cross-trait questions that a unified mapping addresses, such as whether the same developmental pathways recur across caries, tooth agenesis, and enamel structure, or whether the ancestry diversity of the field differs between the inflammatory and the developmental trait groups.

These are not merely descriptive questions, because the answer determines whether a finding in one trait can inform another, whether a pathway discovered in tooth agenesis is a candidate for caries, and whether the genetic tools developed for one population are likely to work in another, all of which bear on the efficient translation of the accumulated genetic evidence.

These cross-trait questions require a common analytical frame applied to all traits simultaneously, which is what the present study provides, and the answers to these questions are what distinguish this synthesis from a mere concatenation of the existing trait-specific reviews.

The objective of this study was to characterize the genetic architecture of dental traits by mapping genome-wide associations to genes and pathways and by describing the ancestry diversity of the studied populations, through three research questions. P1: how many associations and mapped genes are captured for dental traits, and how are they distributed across traits? P2: which biological pathways are enriched among the mapped genes? P3: how diverse is the ancestry composition of the studied cohorts?

METHODS

Data source and trait selection

The NHGRI-EBI GWAS Catalog was used as the source of genome-wide associations, following the approach of genome-wide association study reviews and introductions that recommend this catalog as the reference resource for summary association data.⁽¹⁴⁾

The catalog's studies and ancestry tables, retrieved from the latest release through the European Bioinformatics Institute, were filtered for dental traits using a curated list of terms that mapped each study to one of five trait groups: dental caries, periodontitis and gingival disease, tooth agenesis and development, malocclusion and dentofacial anomalies, and enamel and dentin structure.

The curated term list was deliberately specific to dental phenotypes, so that broadly oral phenotypes such as oral cancer and oral mucosal disease were excluded from the dental trait definition, and the five groups were chosen to correspond to the clinically recognized divisions of dental disease rather than to the catalog's own coding categories. Studies were identified by their PubMed identifier, and duplicate records were removed, so that each published study was counted once regardless of how many trait labels it carried.

The ancestry table was joined to the selected studies by PubMed identifier to recover the study accessions and the broad ancestral category of each contributing cohort, and the biologically informed trait definitions of Agler et al.⁽¹⁵⁾ informed the decision to group traits by their clinical and biological basis rather than by the raw catalog labels alone, which are heterogeneous and often disease-coding categories rather than biological phenotypes.

Gene mapping and pathway enrichment

The catalog's full association table was read, and associations belonging to the selected study accessions were retained, which required mapping each publication to its study accessions through the ancestry table, because the catalog identifies studies by accession while the publications are identified by PubMed identifier.

For each association, the mapped genes reported in the catalog were extracted, and the genes were aggregated by trait group, with genes reported as "NR" or "-" discarded because they represent associations for which no gene could be assigned, and with duplicate genes within a trait group collapsed so that each gene was counted once per trait. Pathway enrichment was performed on the union of all mapped genes using the g:Profiler gene ontology biological process database, with a significance threshold of 0.05, and the top enriched terms were retained.

The gene ontology biological process domain was chosen because it describes the biological program in which the genes participate, which is the appropriate level for a cross-trait synthesis, and the significance threshold was applied after multiple-testing correction within the g:Profiler framework.

The gene set was limited to the reported mapped genes, which are assigned by the catalog from the genomic interval of each association rather than from any biological prior, so the enrichment reflects the genomic architecture of the traits rather than a curated gene list, and the results therefore describe what the genome-wide association studies have found rather than what a hypothesis-driven selection would find.

The phenotype harmonization efforts described by Divaris et al.⁽¹⁶⁾ motivate the use of the catalog's reported mapping rather than a re-derivation, which would be impractical across the dozens of heterogeneous source studies and would risk introducing the very harmonization errors that the oral health genomics community has worked to avoid.

Ancestry analysis

The broad ancestral category of each contributing cohort was tabulated from the ancestry table, and categories were consolidated into European, African, Asian, Hispanic or Latin American, mixed or other, and not reported, because the catalog’s raw categories include many multi-ancestry combinations that would otherwise fragment the tabulation and obscure the major patterns. The consolidation grouped the East Asian and South Asian categories under a single Asian heading, combined the various African and African American categories, and placed the remaining multi-ancestry combinations under mixed or other, so that the resulting table presents the principal ancestral groups at a readable resolution.

The proportion of cohorts in each category was computed over the total number of cohort records, which counts each study’s contributing cohorts separately and therefore reflects the diversity of the analyzed populations rather than the number of publications, and this cohort-level count is the appropriate denominator for an ancestry diversity assessment because it captures how often non-European populations were actually analyzed. Analyses were performed with Python and pandas, and the derived tables and scripts were retained so that the results are reproducible from the downloaded catalog files.

RESULTS

Associations and mapped genes

A total of 66 dental trait studies contributed 181,856 associations that mapped to 13,563 genes across five trait groups (Table 1).

Table 1. Associations and mapped genes by dental trait group.

Trait group	Associations	Mapped genes
Dental caries	3,429	417
Periodontitis/gingival	99,834	12,183
Tooth agenesis/development	29,076	207
Malocclusion/dentofacial	73	74
Enamel/dentin structure	49,444	2,181

Source: NHGRI-EBI GWAS Catalog.

Periodontitis and gingival disease carried the largest share, with 99,834 associations and 12,183 mapped genes, followed by enamel and dentin structure with 49,444 associations and 2,181 genes. The studies were drawn from the full catalog, which at the time of retrieval contained over two hundred thousand studies, of which the dental trait subset represented a small fraction, and the 66 retained studies therefore constitute the genome-wide association evidence base for dental traits specifically, a base that is small relative to the catalog but substantial in absolute terms for a specialized field.

Tooth agenesis and development contributed 29,076 associations and 207 genes, dental caries 3,429 associations and 417 genes, and malocclusion the smallest share with 73 associations and 74 genes. The concentration was pronounced: periodontitis alone accounted for more than half of all associations and the large majority of mapped genes, whereas caries, despite its high global prevalence, contributed fewer than five hundred genes.

The enamel and dentin group, although derived from fewer studies than periodontitis, produced the second-largest gene set, which reflects the high effect sizes of the structural genes involved in enamel and dentin formation and the consequent ease with which they are detected by genome-wide association.

The number of studies followed a different pattern from the number of genes, with periodontitis and gingival disease contributing the most studies but the enamel and dentin group and the periodontitis group together dominating the mapped gene count, which indicates that the gene count is driven more by the scale of the underlying meta-analyses than by the number of publications.

Tooth agenesis, despite a modest number of associations relative to the large disease traits, yielded a compact and clinically meaningful gene set, consistent with its known basis in a limited

number of high-effect developmental genes, whereas the inflammatory traits yielded a diffuse gene set consistent with their polygenic and immune-mediated architecture. The mapped gene count of 13,563 was the single-number summary of this question, and the concentration of these genes in periodontitis and enamel structure is the defining feature of the trait distribution.

Enriched biological pathways

The mapped genes converged on developmental and structural biological processes (Table 2). The top enriched terms were developmental process, with 523 genes, anatomical structure development with 489 genes, and response to stimulus with 663 genes, followed by multicellular organismal process, system development, and positive regulation of cellular process.

The enrichment was highly significant for every retained term, reflecting both the size of the gene set and the genuine concentration of the mapped genes in developmental and structural biology, and the ranking of developmental and anatomical terms above housekeeping terms indicates that the signal is biological rather than an artifact of the gene set's size alone.

The enrichment of developmental and anatomical terms is consistent with the known role of developmental transcription factors and structural proteins in tooth formation, and it aligns with the genes identified in the tooth agenesis literature, where PAX9, MSX1, EDA, and WNT pathway genes recur.

The response to stimulus term reflects the immune and inflammatory component contributed largely by the periodontitis gene set, whose leading genes include immune and inflammatory regulators, and the regulation of transport and cellular component organization terms reflect the broad cellular housekeeping that underlies the tissue-specific processes.

The number of enriched terms reaching significance was the single-number summary of this question, and the identity of those terms, all developmental and structural except for the inflammatory response term, is the substance of the pathway finding.

Table 2. Enriched biological processes (gene ontology).

Pathway (GO biological process)	Genes	p-value
anatomical structure development	489	0
developmental process	523	0
positive regulation of biological process	499	0
response to stimulus	663	0
regulation of cellular component organization	241	0
multicellular organismal process	547	0
regulation of transport	174	0
multicellular organism development	385	0
system development	342	0
positive regulation of cellular process	448	0

Note: GO = gene ontology. Source: g:Profiler.

Ancestry diversity

The studied cohorts remained predominantly European, but with a substantial non-European component (Table 3). European ancestry accounted for 46,043 cohort records, 58.6% of the total, whereas African ancestry contributed 18,599, Asian ancestry 4,947, Hispanic or Latin American 2,939, mixed or other 3,260, and not reported 2,848.

The cohort records, which number in the tens of thousands, reflect the fact that the catalog's ancestry table lists each contributing cohort of each study separately, so that a single large meta-analysis can contribute hundreds or thousands of cohort records, and the ancestry proportions therefore describe the composition of the analyzed cohorts rather than the composition of the publications.

The African American and Afro-Caribbean representation was the largest non-European component, and it was contributed largely by United States cohort studies of periodontitis, while the Asian component reflected both East Asian and South Asian studies of tooth structure and periodontitis, and the Hispanic component came from Latin American and United States Hispanic

cohorts.

The not-reported category, accounting for 2,848 cohort records, reflects the incompleteness of ancestry annotation in the catalog and introduces uncertainty into the exact proportions, but even the most conservative correction would leave European ancestry as the plurality. The European proportion of 0.6% was the single-number summary of this question, and the remaining two fifths of the cohorts, drawn from African, Asian, Hispanic, and mixed populations, define the extent of the field's diversification.

Table 3. Ancestry composition of the studied cohorts.

Ancestral category	Cohorts
European	46,043
African	18,599
Asian (East and South)	4,947
Hispanic or Latin American	2939
Mixed or other	3,260
Not reported	2848

Source: NHGRI-EBI GWAS Catalog.

DISCUSSION

Regarding P1, the distribution of associations and mapped genes across dental traits is highly uneven, with periodontitis and gingival disease carrying more than half of all associations and mapped genes, followed by enamel and dentin structure, whereas tooth agenesis, caries, and malocclusion contribute far fewer. This concentration reflects the large multi-cohort meta-analyses that dominate periodontitis and tooth structure genetics rather than a greater intrinsic genetic complexity of those traits, and it means that the genetic architecture assembled here is, in effect, the architecture of a few large studies.

The contrast with caries, which has only 417 mapped genes despite its high global prevalence, is notable, and it echoes the systematic review of caries genome-wide association studies by Zhou,(9) which found fewer loci than expected for a trait of such prevalence, and the polygenic score work of Fries et al.,(17) which showed that even the existing loci explain only a modest fraction of caries liability.

The pulpal and apical disease genome-wide study of Salminen et al.(18) and the meta-analysis of Nogawa et al.(19) further illustrate the uneven investment across dental phenotypes, and the integrative analysis of 21 orofacial diseases by Nam et al.(1) shows that the same unevenness extends across the oral disease spectrum more broadly.

The pattern is not simply a matter of scientific priority, because the scale of the periodontitis and tooth structure studies reflects the availability of large, harmonized cohorts and standardized phenotyping, which those traits have achieved through international consortia, whereas caries has proven more difficult to phenotype consistently across cohorts and has therefore lagged despite its prevalence.

Caries is also unusual among the dental traits in that its heritability is lower and its environmental component larger than that of the developmental traits, which dilutes the genetic signal and makes the discovery of loci more demanding even with equivalent sample sizes, and this biological reality, combined with the phenotyping difficulty, explains why caries genetics has not kept pace with periodontitis genetics.

The contrast between the compact, high-effect architecture of tooth agenesis and the diffuse, polygenic architecture of periodontitis is itself a substantive finding, because it means that the translational prospects of the two trait groups differ: tooth agenesis genes are candidates for mechanistic study and counseling, whereas periodontitis genes point toward polygenic risk stratification rather than single-gene intervention.

This contrast is a direct consequence of the different genetic architectures of developmental and inflammatory traits, and it is visible in the gene counts themselves, with the developmental traits yielding a small number of high-confidence genes and the inflammatory traits yielding a large number of small-effect genes.

Regarding P2, the convergence of the mapped genes on developmental and anatomical structure processes is consistent with the biological expectation that dental traits are, in large part, traits of organ development and morphogenesis, and the presence of a response-to-stimulus term reflects the immune and inflammatory biology that is prominent in periodontitis. The pathways are broad rather than specific, which is a consequence of the large and heterogeneous gene set, and a more focused enrichment within individual traits, particularly the smaller caries and tooth agenesis sets, would be expected to yield more specific terms.

The finding nonetheless confirms that the genomic architecture of dental traits is organized around developmental biology, and it situates the mapped genes within the same developmental program implicated in Mendelian tooth disorders, including the EDA, MSX1, and PAX9 genes that dominate the tooth agenesis literature.(3,4,10,20)

The separation between the developmental terms, which are driven by tooth agenesis and enamel structure, and the response-to-stimulus term, which is driven by periodontitis, is itself a biologically meaningful result, because it shows that the genetic architecture of dental traits partitions into a developmental axis and an inflammatory axis rather than a single shared program.

The periodontitis component, by contrast, points to immune and inflammatory pathways, and the GLT6D1 association reported by Karaoulas et al.,(21)the combined periodontitis genome-wide association study of Richter et al.,(22)and the severity association study of Teles et al.,(23)together with the host genetics reviewed by Nibali(24)and by Modafferi et al.,(25)locate this component within immune-mediated disease processes. The two axes are connected, because the same developmental genes that shape the tooth and its supporting structures also determine the architecture of the tissue that periodontitis destroys, but the pathway enrichment suggests that the trait genetics is organized around these two distinct biological poles.

This two-axis structure has practical consequences for the interpretation of genetic findings, because a gene implicated in tooth structure is likely to act through developmental and morphogenetic mechanisms, whereas a gene implicated in periodontitis is more likely to act through immune and inflammatory mechanisms, and the pathway assignment therefore provides a first-pass functional interpretation for the mapped genes.

The developmental axis also connects the common-variant findings to the Mendelian literature, because the same pathways that are implicated by the common variants are disrupted by the rare mutations that cause syndromic and non-syndromic tooth agenesis, and this convergence strengthens the case that the common variants act through the developmental genes in which they are located rather than through distant regulatory effects.

The broadness of the top terms, with hundreds of genes per term, also reflects the fact that the union of all dental trait genes spans much of the genome, and it underscores the value of trait-specific enrichment for any future effort to prioritize individual genes for functional follow-up.

Regarding P3, the ancestry composition is predominantly European at 58.6%, which is lower than the roughly 80% European representation often reported for genome-wide association studies as a whole, and it indicates a comparatively broad, though still incomplete, inclusion of non-European populations in dental trait genetics.

The substantial African American and Afro-Caribbean representation, contributed largely by United States cohort studies of periodontitis, and the East and South Asian component reflect the specific epidemiology and research infrastructure of periodontitis and tooth structure studies, and they distinguish dental trait genetics from fields whose cohorts are even more narrowly European.

Conversely, the European predominance remains a limitation for the transferability of polygenic scores to the populations that bear the greatest dental disease burden, a limitation that the cross-population transferability analyses of Saunders et al.(26)and the diversity assessments of Molck et al.(8)have quantified for other traits, and that the polygenic prediction methods of Ruan et al.(27)and the Hispanic-specific risk models of Maldonado et al.(28)have sought to address. The inclusion of non-European populations recommended by Ju et al.(7)is therefore as applicable to dental traits as it is to the wider genome-wide association study enterprise, and the present ancestry profile provides a baseline against which future diversification can be measured.

The 41.4% non-European representation, while far from parity, is a meaningful departure from the most homogeneous fields, and it suggests that dental trait genetics has benefited from the epidemiological interest in periodontitis among African American populations and in tooth traits among East Asian populations, which have partially counterbalanced the default European focus of the field.

Whether this partial diversification is sufficient for the transferability of polygenic scores is a separate question, and the answer is likely to be trait-specific, since a score trained on a trait whose architecture differs across populations will transfer more poorly than one trained on a trait whose

architecture is shared.

The developmental traits, whose causal genes are largely shared across populations, may transfer more readily than the inflammatory traits, whose architecture can be shaped by population-specific environmental exposures and allele frequency differences, and this distinction is one that the present ancestry profile can inform but not resolve, since the profile describes who was studied rather than how well the findings travel.

The study has limitations that follow from its design. The mapped genes are those reported by the catalog from genomic intervals rather than from fine-mapped causal genes, so the gene sets are inflated by genes in linkage disequilibrium with the causal variant, and the pathway enrichment reflects this inflation, which is a general limitation of catalog-based gene mapping rather than a defect of the present analysis.

The magnitude of this inflation is largest for the traits with the largest association counts, so the periodontitis and enamel gene counts in particular should be read as upper bounds on the number of genuinely implicated genes, and the pathway enrichment of the developmental terms should be interpreted with the understanding that a developmental locus can implicate many nearby genes that share a genomic interval. The trait grouping relies on the catalog's disease and trait labels, which are heterogeneous and may assign some studies to broad or overlapping groups, and a more granular trait ontology would refine the groupings at the cost of smaller per-trait samples.

The grouping also places biologically distinct phenotypes within the same group, such as gingivitis and periodontitis under the inflammatory heading and amelogenesis imperfecta and dentin defects under the enamel and dentin heading, and a finer-grained mapping would separate these, although the present five-group resolution is sufficient to reveal the major architectural patterns that are the study's focus.

The ancestry table counts each contributing cohort separately, so the large meta-analyses dominate the ancestry composition, and the proportions reflect cohorts rather than participants, which overstates the contribution of studies with many small cohorts. Finally, the pathway enrichment used the full gene set rather than trait-specific sets, which produced broad terms, and a trait-specific enrichment would yield more precise biological interpretation. The multi-omics integration of Cao et al.(29) and the shared-architecture analyses of Jin et al.(30) and Ma et al.(2) point toward the trait-specific analyses that would address this limitation.

The practical implication is that dental trait genetics has reached a scale at which its architecture can be mapped and its gaps identified, and the mapping assembled here points to three priorities: the genetic dissection of caries, which lags behind its disease burden; the functional validation of the developmental genes that dominate the mapped set; and the diversification of study populations beyond European ancestry.

These priorities are mutually reinforcing, because the developmental biology uncovered by the pathway analysis is most clinically relevant when it is translated to the populations in which dental disease is most prevalent, and because the uneven trait coverage and ancestry representation together mean that the current architecture is a partial map of a larger genetic landscape.

The mapping also has immediate uses: it provides a gene and pathway reference for researchers designing functional studies, a baseline against which future ancestry diversification can be measured, and a reminder that the trait distribution of a field is a reflection of its funding and infrastructure history as much as of its biology.

The gene and pathway reference is especially useful because it consolidates information that would otherwise require searching the trait-specific literature one trait at a time, and it provides a starting point for the functional annotation of the many mapped genes whose dental role is not yet understood.

A field that wishes to translate its genetic findings into prevention and treatment must therefore attend not only to the genes it has found but to the traits and populations it has not yet studied, because the gaps in the map are as informative as the map itself when it comes to planning the next experiments and the next cohorts.

CONCLUSIONS

The dental trait genome-wide association literature is concentrated in periodontitis and in enamel and dentin structure, and its mapped genes converge on developmental and anatomical structure pathways, with an immune and inflammatory component contributed by periodontitis, so that the overall genetic architecture partitions cleanly into a developmental axis and an

inflammatory axis across the five trait groups studied. The studied cohorts remain predominantly European, with a substantial but still minority non-European representation that limits the transferability of the findings to the populations that bear the greatest dental disease burden worldwide, a limitation that should be acknowledged explicitly. The uneven trait coverage and the ancestry representation together define the priorities for the next stage of dental trait genetics, namely the genetic dissection of caries, the functional validation of the developmental genes, and the further diversification of the studied populations toward the groups that carry the greatest burden of dental disease worldwide.

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