

Systematic Review

Single-Nucleotide Polymorphisms Associated with Paediatric Oral Phenotypes: A Systematic Review and Candidate Panel Design for Precision Prevention

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Abstract

Introduction: Genetic susceptibility shapes paediatric oral health, yet candidate variants remain scattered across phenotype-specific studies. **Aim:** To synthesise genetic association evidence for oral and craniofacial phenotypes with paediatric onset, and to propose a candidate single-nucleotide polymorphism (SNP) panel to inform future risk-stratification research supporting precision prevention in paediatric dentistry. **Methodology:** A PRISMA 2020-informed systematic search of PubMed, Web of Science, and Scopus (2015–2024) identified genome-wide association studies (GWASs), meta-analyses, and replicated candidate-gene studies reporting SNP-phenotype associations for paediatric oral traits. Variants were assigned to five trait clusters and graded Strong, Moderate, or Weak against pre-specified replication, study design, and effect-estimate criteria. Phenotypic, population, and methodological heterogeneity precluded quantitative pooling; narrative synthesis was performed. **Results:** The candidate panel comprises 22 SNPs across five trait clusters: eruption and number; morphology, agenesis, and craniofacial growth; enamel structure and caries; periodontal inflammation; and pain sensitivity. Twelve variants (Tier 1) meet genome-wide significance or meta-analytic replication thresholds; ten (Tier 2) have moderate or exploratory evidence, designated for research-grade use pending prospective paediatric validation. **Conclusion:** This evidence-graded 22-SNP panel offers a reproducible candidate framework for future genetic risk-stratification research in paediatric dentistry, not a validated clinical test. Prospective multicentre validation, population-level calibration, and implementation studies are required before clinical adoption. The article reports a systematic evidence synthesis and panel design rationale, not assay or clinical validation data.



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1. Introduction

Single-nucleotide polymorphisms (SNPs) with replicated associations may inform future research on oral-disease risk stratification and DNA-informed prevention [1,2]. Current preventive protocols focus predominantly on behavioural and environmental modification, yet genetic factors account for a substantial proportion of variance in caries susceptibility, tooth morphology, periodontal inflammatory response, and craniofacial

development [1,2]. The SNP panel concept provides a framework for evaluating whether evidence-graded genetic markers could eventually be integrated into paediatric dental research pathways.

GWASs and meta-analyses link common SNPs to early childhood caries [3–5], tooth eruption timing [6], enamel thickness [7], craniofacial growth and malocclusion [8,9], periodontal inflammation [10,11], and pain sensitivity [12]. Candidate-gene and sequencing studies have reported associations between common or rare variants and several paediatric oral phenotypes [13–18]. Uptake in practice remains limited. This article addresses the molecular biology of these associations: the functional mechanisms by which sequence variants alter enamel matrix assembly, transcription factor binding at immune-gene enhancers, cytokine output, and catecholamine metabolism, and the biological consequences for oral tissue development and disease susceptibility in childhood.

Despite this accumulating evidence, several gaps limit its translation into paediatric practice. First, published associations remain scattered across domain-specific reports, with no systematic synthesis spanning enamel biology, eruption timing, immune modulation, craniofacial growth, and pain sensitivity simultaneously. Second, existing reviews rarely apply explicit, pre-specified evidence grading to distinguish genome-wide replicated variants from single-study candidate-gene findings, leaving clinicians and researchers without a transparent basis for prioritising markers. Third, no previous work has proposed a reproducible SNP selection algorithm that formally documents inclusion and exclusion decisions, making prior candidate panels difficult to evaluate or update as new evidence emerges. Fourth, attribution of effect estimates to the correct primary GWAS source is essential to avoid propagating misattributed risk allele coding through downstream applications.

The present systematic evidence mapping addresses these gaps in four ways. It provides a guided synthesis spanning paediatric oral-genetic domains consolidated into five trait clusters, with pre-specified eligibility criteria and a four-step SNP selection algorithm documented in full (Supplementary File S1). It applies explicit evidence grades (Strong, Moderate, Weak) and a two-tier operational classification to each of the 22 candidate variants, separating genome-wide or meta-analytically replicated markers (Tier 1) from those requiring further paediatric validation (Tier 2). It aligns the allele-coding throughout the panel with the original Munz et al. [19] GWAS report (rs4284742 G as the risk allele, OR 1.34, 95% CI 1.21–1.48), with explicit citation of the GWAS source rather than the functional follow-up by Mueller et al. [11], which validated the regulatory mechanism but does not itself report effect estimates. Finally, it provides a documented rejected-variant list (Supplementary Table S5) that makes the selection process auditable and updatable as discovery science advances. The SNP panel should be understood not as a validated diagnostic service but as a translational proposal intended to organise available evidence and support future prospective testing of genotype-informed preventive pathways.

A conceptual translational pathway linking the candidate panel to future paediatric dental care is outlined in Section 4: (i) collect a buccal swab at the first well-child dental visit; (ii) perform targeted genotyping of the 22-SNP panel; (iii) explore descriptive domain-level profiles using published effect-size weights and evidence grades; (iiii) develop candidate decision-support materials for prospective evaluation and a plain-language parent summary covering dietary advice, fluoride protocols, eruption monitoring, and orthodontic referral timing. If prospectively validated, genotype-informed preventive decisions may improve the timing and targeting of paediatric oral-health interventions.

The 22 variants meeting pre-specified criteria for replication, biological plausibility, and paediatric relevance form five trait clusters summarised in Table 1.

Table 1. Trait clusters, illustrative genes/loci, and genetic rationale for inclusion of variants in the paediatric oral-health SNP panel.

Trait Cluster	Illustrative Genes/Loci	Genetic Rationale for Inclusion	References
Enamel structure and caries	<i>ENAM, AMELX, MMP20, KLK4, ALLC, NEDD9, VDR, TAS2R38</i>	SNPs in enamel-matrix structural genes and proteases are associated with enamel thickness and caries susceptibility across multiple paediatric cohorts and meta-analyses; taste-receptor and vitamin-D-pathway variants contribute via sugar preference and mineralisation pathways.	[3,4,20,21]
Tooth eruption and number	<i>ADK, HMGA2, CALU</i>	GWAS loci and replicated candidate-gene variants at eruption-timing and morphogenesis genes flag children at risk of delayed eruption, hypodontia, or arch-length discrepancy requiring early radiographic monitoring.	[1,6,22,23]
Periodontal inflammation	<i>IL1A, IL1B, SIGLEC5</i>	Cytokine and inhibitory-receptor variants modulate host response to supragingival biofilm; carriers of high-risk genotypes at these loci show consistently elevated periodontitis odds across meta-analyses and functional fine-mapping studies.	[11,19,24,25]
Tooth morphology and agenesis, including craniofacial growth and malocclusion	<i>WNT10A, EDAR, PAX9, AXIN2, MYO1H, NOG</i>	Cytoskeletal (<i>MYO1H</i>) and BMP-antagonist (<i>NOG</i>) variants associate with mandibular growth variation, including prognathism and micrognathia; early identification may support timely craniofacial monitoring before the pubertal growth spurt.	[8,9]
Pain sensitivity	<i>COMT</i>	A catechol-O-methyltransferase variant modulating catecholamine metabolism is associated with pain thresholds in dental and temporomandibular cohorts; retained as a single research-grade marker pending prospective paediatric validation. Bruxism-specific variants were reviewed but excluded because supporting evidence derives exclusively from adult occupational cohorts without paediatric replication.	[12]

Key gene-trait associations.

Dental caries and enamel integrity. Exome-array screening in Saudi preschoolers identified loss-of-function variants in *ENAM* and *AMBN* among the most severely affected children [13]. A meta-analysis of 24 studies confirmed the risk association at *AMELX* rs17878486 (OR 1.40, 95% CI 1.02–1.93; [14]). A candidate-gene study in 95 Polish children aged 2–3 years (48 caries vs. 47 caries-free) reported high in-sample discriminative ability

for an 8-SNP logistic-regression model (AUC = 0.970, 95% CI 0.912–0.994), with overlapping predictor variants identified by a parallel neural-network analysis [26]; the modest cohort size and lower internal validation accuracy (73.6–87.2% in held-out predictions vs. 90.9–98.4% in the training set) place the estimate in proof-of-concept territory pending replication in larger paediatric samples.

Tooth eruption, size, and agenesis. Common variant *WNT10A* rs10177996 influences crown dimensions, while low-frequency coding alleles in ectodermal genes double the odds of non-syndromic agenesis in Nordic cohorts [16]. Scheduled panoramic imaging supports timely interception of spacing problems in carriers.

Craniofacial growth and malocclusion. *MYO1H* rs10850110 (A>G) is associated with skeletal Class III malocclusion due to mandibular prognathism in a Brazilian candidate-gene cohort, with subsequent evaluation in an Indian cohort. Cruz et al. [27] reported a strong association in a Brazilian sample (n = 54 cases, 120 controls; OR 7.44, 95% CI 4.02–13.77, $p < 0.01$); the wide confidence interval reflects the modest cohort size, and the effect estimate should be interpreted with caution given the well-known winner's-curse bias in small candidate-gene studies. Atteeri et al. [8] examined the association in an Indian cohort (n = 60); the reported $p < 0.0001$ is the Hardy-Weinberg equilibrium test, not a case-control result, and the case-control odds ratios were non-significant with wide confidence intervals, so this study offers only weak support. The variant is retained as Tier 2 (Moderate evidence) pending larger replication and meta-analytic synthesis. A gene-level signal at *DUSP6*, a phosphatase attenuating ERK activity, is reported for sagittal jaw discrepancy [9] without a lead SNP. The retained Tier 2 craniofacial marker at this slot is *NOG* rs1348322, which the same review associates with mandibular micrognathia in four families [9]; no primary cohort odds ratio is available.

Periodontal inflammation. Fine-mapping at 19q13 identifies the G allele at *SIGLEC5* rs4284742 as a GWAS risk allele for periodontitis (OR 1.34, 95% CI 1.21–1.48; [19]; functional validation by [11]); together with cytokine variants in *IL1A* and *IL1B*, these loci define the periodontal sub-index of the SNP panel [10].

Pain sensitivity. The *COMT* Val158Met variant (rs4680) modulates catecholamine metabolism and has been associated with altered pain sensitivity in dental and temporomandibular pain cohorts [12]. It is retained as the sole representative of the pain sensitivity domain; bruxism-specific variants were excluded from the final panel because supporting evidence derives exclusively from adult occupational cohorts without paediatric replication or extractable odds ratios (see Supplementary Table S5).

The SNP panel.

The 22-SNP panel integrates paediatric oral-genetics evidence into an evidence-graded risk-stratification framework conceptualised for future evaluation in preschool-age populations [28]. A conceptual translational pathway is summarised in Figure 1 and discussed in Section 4. The rationale for early genotyping rests on four arguments. First, genotype-informed risk scores could be tested for its ability to identify groups that might benefit from intensified fluoride protocols before irreversible demineralisation occurs. Second, enamel-defect alleles, *PAX9* variants, and high immune-load scores each point to distinct preventive strategies requiring prospective evaluation. Third, risk-stratified recall scheduling could improve resource allocation, though the appropriate threshold and interval require clinical-trial evidence. Fourth, incorporation of new GWAS signals as they emerge could maintain the analytical currency of risk scores without additional sampling [1,2]. Prospective trials are needed to determine whether genotype-guided preventive strategies reduce lesion incidence, treatment burden, and long-term costs [17]. For approximately half of the paediatric oral-health domains represented in the panel, the current evidence base identifies priorities for preventive and monitoring research but does not yet support

genotype-directed decisions, whereas the remaining domains should be regarded primarily as targets for future translational research.

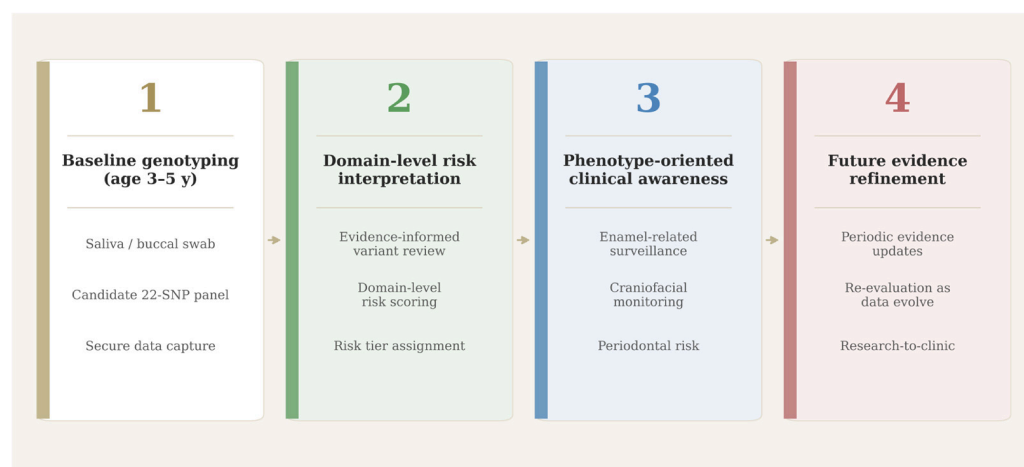


Figure 1. Conceptual four-stage translational pathway for the proposed paediatric oral-health candidate SNP panel. The schematic illustrates a hypothetical route from sample collection to domain-level risk interpretation, phenotype-oriented clinical awareness, and future evidence refinement. It is intended as a conceptual framework only and does not represent a validated clinical workflow, decision-support system, or recall protocol.

2. Methods

2.1. Study Design and Reporting Standard

This study is a systematic evidence mapping with a subsidiary panel construction component. Evidence identification and selection followed a pre-specified protocol (Supplementary File S1). Reporting follows the PRISMA 2020 guidance [29] as applicable to evidence mapping; adaptations to the standard flow are noted where made. The protocol was not registered in PROSPERO, either prospectively or retrospectively. This constitutes a methodological limitation; the absence of registration means that post hoc outcome selection cannot be formally excluded. The mapping was initiated as an evidence-synthesising component of a broader translational project before PROSPERO registration requirements were applied; post hoc registration was not feasible as screening had already commenced. All eligibility criteria, domain definitions, evidence-grading rules, and the SNP selection algorithm were specified before screening commenced and are reported without deviation in Supplementary File S1. One element was refined after screening: the operational two-tier classification described in Section 3.9, which maps the pre-specified Strong, Moderate, and Weak grades onto Tier 1 and Tier 2 and retains a small number of Weak-graded variants within Tier 2, was introduced during revision and is reported here as a post hoc correction rather than a pre-specified rule. The database searches were reconstructed for documentation because the original exportable record sets were not preserved; this limits full computational reproducibility, and future applications of this method should archive raw search exports and screening logs.

2.2. Eligibility Criteria and Search Sources

The target population comprised children and adolescents, or mixed-age cohorts where the phenotype has paediatric onset or actionable surveillance relevance before adulthood. Eligible study designs were genome-wide association studies (GWASs), meta-analyses, and replicated candidate-gene studies reporting at least one SNP-phenotype association with a quantitative effect estimate (odds ratio, beta coefficient, or *p*-value with direction). Outcomes were oral and craniofacial phenotypes across five trait clusters:

(1) tooth eruption and number; (2) tooth morphology and agenesis, including craniofacial growth and malocclusion; (3) enamel formation and caries susceptibility; (4) periodontal inflammation; and (5) pain sensitivity. The original screening framework included bruxism-related traits as a seventh domain; after exclusion of all bruxism-specific variants during evidence grading, the panel consolidates the remaining six phenotypic domains into the five panel clusters by merging craniofacial growth and malocclusion into the tooth morphology and agenesis cluster. Studies were excluded if they reported no quantitative SNP-phenotype association, involved adult-only populations without paediatric phenotype relevance, provided inadequate statistical reporting, or existed only as *in silico* predictions or functional assays without population-level evidence. Reviews, editorials, case reports, and conference abstracts were excluded. Only English-language publications from January 2015 to December 2024 were eligible in the primary search. References dated after this search window (for example [5,30–33]) are cited only for contextual discussion, including background epidemiology, precision-health framing, and directions for future validation, and did not contribute to the formal evidence synthesis, SNP selection, or evidence grading, which drew exclusively on records retrieved between January 2015 and December 2024. Foundational pre-2015 studies (for example [6,15,34]) were identified through citation tracking of eligible post-2015 publications and included under a pre-specified exception; these are recorded separately in the PRISMA flow (Supplementary Figure S1). Full search strategies for PubMed, Web of Science, and Scopus are provided in Supplementary Table S1.

2.3. Selection and Data Extraction

Database searches identified 743 PubMed records, 691 Web of Science records, and 658 Scopus records (2092 in total; 733 duplicates removed, 1359 unique records screened). Two reviewers (K.C. and M.M.) independently screened all titles and abstracts, then assessed full texts against the eligibility criteria. After title and abstract screening, 172 full-text records were assessed; 88 were excluded at the full-text stage, yielding 84 studies in the final synthesis. The PRISMA 2020 flow diagram is provided in Supplementary Figure S1. Disagreements were resolved by discussion and consensus. Inter-rater agreement (Cohen's kappa) was not formally calculated at either screening stage, as decisions were not digitally logged; this precludes quantification of inter-rater agreement and constitutes a methodological limitation. Data were extracted independently by both reviewers using a structured template recording: rsID, gene symbol, phenotype definition, study design, population (ancestry, age range, sample size), effect measure with 95% confidence interval, allele coding, population stratification method, multiple-testing correction, and replication status. The full exclusion list with reasons is provided in Supplementary Table S2; the initial candidate SNP list is in Supplementary Table S3. Characteristics of the individually named included studies are summarised in Supplementary Table S6. Table S6 characterises this named subset of primary evidence sources and translational-context studies, not all 84 included records; a complete study-by-study table for every record was not derivable from the manuscript text alone, as stated in the table caption.

2.4. Risk of Bias and Certainty Assessment

Study-level quality was assessed using two complementary approaches. For candidate-gene studies, the Q-Genie tool [35] was applied by both reviewers independently; study-level Q-Genie scores for individual candidate-gene studies are provided in Supplementary Table S4c. Only total (summed) Q-Genie scores and the resulting overall grades are reported; item-level scores across the eleven Q-Genie domains were recorded during appraisal but are not tabulated here. For GWASs and meta-analyses, key quality indicators were extracted: phenotype definition clarity, genotyping and imputation

quality control, population stratification control, multiple-testing correction strategy, and replication availability. These indicators informed the certainty grade assigned to each SNP-phenotype association using HuGENet dimensions: amount of evidence, replication consistency, and protection from bias; the resulting certainty grades are tabulated in Supplementary Table S4d.

2.5. Data Synthesis and SNP Selection

Phenotypic, population, and methodological heterogeneity across domains precluded quantitative pooling; findings are presented as a structured narrative synthesis. SNP selection followed a four-step algorithm (Supplementary File S1, Section S1.7): (1) all eligible SNP-phenotype associations were recorded in the candidate list; (2) SNPs were deduplicated by rsID and assigned to one of five trait clusters; (3) each association was graded Strong, Moderate, or Weak using pre-specified criteria; and (4) within each domain, variants were prioritised by evidence strength, paediatric onset relevance, and multiplex genotyping feasibility. Where evidence for two variants at the same locus was comparable, the variant with the more precise effect estimate or broader cross-ancestry replication was retained. Rejected candidates with rationale are listed in Supplementary Table S5. Extracted effect estimates per SNP are provided in Supplementary Table S4. The final panel size (22 variants) was not fixed in advance; it is the number of variants that passed all four selection steps across the five trait clusters, reflecting evidence thresholds, paediatric relevance, and multiplex genotyping feasibility rather than a predetermined target.

3. Results

Genotype-phenotype associations in paediatric oral health.

Twenty-two SNPs published between 2011 and 2024 were selected from GWASs, candidate-gene analyses, and meta-analyses. Each variant was assigned to a primary trait cluster, with pleiotropic effects noted where relevant. Findings are presented thematically according to the principal phenotypic categories affected.

3.1. Tooth Development and Eruption Timing

Tooth number, morphology, and eruption schedule display strong heritability through the orchestrated action of patterning and signalling genes. A GWAS identified *ADK* rs7924176; the allele linked with delayed permanent eruption corresponded to fewer teeth present at matched chronological age [6]. Common variant *WNT10A* rs10177996 influences crown dimensions, while rare and low-frequency variants in the same gene contribute to a substantial proportion of non-syndromic tooth agenesis: in a cohort of selective tooth agenesis patients, 40% carried at least one *WNT10A* mutation, with bi-allelic carriers showing severe agenesis and heterozygotes showing mild phenotypes or no apparent phenotype [23]. Scheduled panoramic imaging supports timely interception of spacing problems in carriers. The ectodysplasin pathway also modulates morphology; the *EDAR* missense variant rs3827760 (Val370Ala) increases the expression of shovel-shaped incisors in an additive manner, explaining roughly 19% of phenotypic variance and altering crown-size ratios [34]. Pathway-level analyses have further explored ectodysplasin-pathway variation in early dental development [6,16].

Transcription factor *PAX9* directs odontogenesis; rare mutations cause familial oligodontia, while common variants modulate tooth number in the broader population. In Turkish children, the promoter SNP *PAX9* rs2073247 (-1031 G>A) combined with -912C formed a haplotype associated with lower hypodontia risk, whereas the G-1031/T-912 combination was enriched among affected cases [36]. Other odontogenesis-related candi-

dates, including *MSX1* rs12532, were reviewed but not retained because replication was inconsistent (Supplementary Table S5).

Within the Wnt axis, the missense variant *AXIN2* rs2240308 (P50S) is associated with selective incisor agenesis and may also affect craniofacial proportions [37]. Eruption timing follows a polygenic pattern; within the present evidence base, *ADK* rs7924176 provides the strongest direct GWAS support for variation in permanent tooth eruption timing [6].

Prospective studies should determine whether genotyping these loci adds value to conventional radiographic monitoring and space-management decisions.

3.2. Enamel Structure and Caries Susceptibility

Genetic control of matrix secretion and proteolytic processing shapes enamel hardness and thickness. SNPs in *ENAM* and *AMBN*, encoding enamelin and ameloblastin respectively, have been examined as determinants of structural weakness and caries onset. Homozygous carriers of the A allele at *ENAM* rs12640848 show elevated early-childhood caries odds in the meta-analysis by Sharma et al. [3]; effect estimates across included studies ranged from approximately OR 2–3. Two meta-analyses directly conflict for *ENAM* rs12640848: Sharma et al. [3] report elevated early-childhood caries odds (OR range 2–3), whereas Li et al. [14] find no significant association (OR 1.15, 95% CI 0.88–1.52, $p = 0.310$). This contradiction is unresolved. The Strong/Tier 1 grade rests on Sharma et al. [3] as the most recent synthesis, and the conflicting evidence is carried forward explicitly wherever rs12640848 is interpreted (Table 2 note; Supplementary Table S4). Daubert et al. [7] reported thinner enamel in carriers of the derived allele at *ENAM* rs7671281 in an African American cohort, supporting a broader link between *ENAM* variation and enamel structure. *AMBN* rs4694075 was excluded from the final 22-SNP panel: peer-reviewed evidence for *AMBN* variants and caries is inconsistent. Wang et al. [38] tested 23 SNPs in 14 genes, including *AMBN* rs13115627, in 1055 South Chinese adolescents; the *AMBN* signal did not survive Bonferroni correction. A meta-analysis of eight studies likewise found no significant pooled association [20]; the variant is catalogued in Supplementary Table S5 pending peer-reviewed replication.

Proteolytic enzymes completing enamel maturation introduce an additional layer of structural vulnerability. *MMP20* rs1784418 carriers show roughly a 10% increase in early-childhood caries risk across diverse populations [3]; limited cleavage of matrix proteins may weaken prism architecture. A comparable risk increment is observed for the serine-protease variant *KLK4* rs2242670 in European and Egyptian cohorts [4]. A separate meta-analysis [14] found no significant association for *MMP20* rs1784418 (OR 1.07, 95% CI 0.76–1.49, $p = 0.702$); the Strong/Tier 1 classification relies on Sharma et al. [3] but this discrepancy should be disclosed when interpreting panel outputs.

Evidence for genes guiding matrix assembly is less consistent. A meta-analysis identified *TUFT1* as a candidate [20], yet no signal emerged for the same locus in an Egyptian replication study, illustrating population heterogeneity [4].

Mineral transport and salivary buffering provide an additional pathway. A genome-wide significant signal near *CA12* (carbonic anhydrase XII; rs11170448, p approximately 2.8×10^{-17}) links impaired salivary pH regulation to hypomineralised enamel through a mechanism independent of matrix proteins [1]; this variant was not retained in the final panel because independent paediatric replication is lacking (Supplementary Table S5).

3.3. Immune-Related Risk of Caries and Periodontal Disease

Genetic variation in innate-immunity and salivary-function genes modulates host-microbiome interactions and mucosal inflammation, shaping susceptibility to caries and periodontal disease despite shared environmental influences such as diet and hygiene [1,39].

The *IL-1* gene cluster illustrates this link. A meta-analysis reported that the *IL1B* +3954 C>T polymorphism (rs1143634) elevates chronic-periodontitis risk in predominantly Asian adult cohorts (pooled OR approximately 1.6 for T-carriers; [10]); this estimate should not be extrapolated to European paediatric populations without ancestry-stratified replication. Small paediatric studies report a directionally consistent increase in caries experience for TT homozygotes. For *IL1A*, the -889 C>T variant (rs1800587) raises periodontitis odds by approximately 22% [24]. High-production IL-1 genotypes may intensify inflammatory responses within dentinal lesions, potentially altering secondary-dentin deposition and pain perception.

Fine-mapping of the *SIGLEC5* locus identified rs4284742 and rs11084095 as candidate causal variants [11]. At rs4284742, the common G allele is the GWAS risk allele for periodontitis (OR 1.34, 95% CI 1.21–1.48; [19]). Mueller et al. [11] showed that this risk allele binds MAFB with strong affinity and drives strong enhancer activity in luciferase reporter assays, whereas the minor A allele reduces MAFB binding by 69% and lowers enhancer activity roughly 9-fold. At rs11084095, the minor A allele abrogates ERG binding. CRISPR-dCas9 activation of the rs4284742 regulatory region in HeLa cells increased *SIGLEC5* expression, validating *SIGLEC5* as the target gene. The functional model proposes that elevated *SIGLEC5* expression in carriers of the G allele impairs discrimination of DAMPs and PAMPs during tissue healing, contributing to the inflammatory phenotype seen in stage III, grade C periodontitis.

A genome-wide analysis of primary dentition identified rs1594318, an intronic variant within the *ALLC* locus, as a caries risk allele [2]. Although *ALLC* does not encode a functional protein in humans, the GWAS signal ($p = 4.13 \times 10^{-8}$; [2]) was identified in a consortium-based paediatric GWAS (up to 19,003 children aged 2.5–18 years across nine cohorts); the causal regulatory mechanism has not been characterised in the primary study, and this locus is classified here as a GWAS signal of uncertain mechanism, consistent with the designation in Supplementary Table S4. Shungin et al. [1] reported that a low-frequency missense variant in *WNT10A* (rs121908120) is associated with lower caries burden, with the A allele corresponding to approximately 2.1 fewer affected tooth surfaces in adults (OR 0.85 for dentures, 95% CI 0.82–0.88), consistent with *WNT10A*'s role in enamel and dentine development.

Whether genotype information can improve the targeting of biofilm-control measures requires prospective paediatric evaluation. Other innate-immunity loci reviewed but not retained (for example *DEFB1*, *MBL2*, and *MUC5B*) showed heterogeneous or insufficiently reproducible associations across populations [39] (Supplementary Table S5).

3.4. Dentin Biology and DSPP-Related Phenotypes

Dentin genetics remains less mapped than enamel biology, and current findings in this domain remain exploratory. Rare loss-of-function mutations in *DSPP* produce dentinogenesis imperfecta, whereas common *DSPP* variants have not shown a reproducible link to hypersensitivity. Genes involved in nociception carry more weight here. *COMT* encodes catechol-O-methyltransferase, a regulator of catecholamine-mediated pain signalling. The Val158Met substitution (rs4680) lowers enzymatic activity in Met carriers and has been associated with heightened temporomandibular pain in adult cohorts. In a dental cohort, a haplotype tagged by rs4818, in linkage with rs4680, correlated with lower oral-pain reports, consistent with *COMT*'s role in pain modulation [12].

Ion-channel genes contribute to nociceptive thresholds but are not represented in the 22-SNP panel. *SCN9A* rs6746030 (Nav1.7 sodium channel) heightens pain sensitivity in temporomandibular disorder cohorts [12], and *TRPV1* (capsaicin receptor) has theoretical

relevance to dental pulp thermal signalling; both were excluded owing to insufficient paediatric dental specificity (Supplementary Table S5).

The panel retains *COMT* rs4680 as an exploratory marker of pain sensitivity, based on evidence from adult dental and temporomandibular pain cohorts; prospective paediatric studies are needed before any genotype-guided analgesic or desensitising strategy can be recommended. The cited oral-pain study [12] genotyped the linked *COMT* variants rs4818 and rs6269 rather than rs4680 directly; rs4680 is retained as the canonical Val158Met marker, and its pain association derives from the broader temporomandibular-pain literature. At present, pain management during paediatric dental care should continue to rely on standard clinical assessment rather than genotype.

3.5. Genetic Risk of Periodontal Inflammation

Cytokine variants.

The composite genotype *IL1A* -889 T + *IL1B* +3954 T heightens interleukin-1 output and amplifies host responses to plaque. Meta-analyses in predominantly Asian adult cohorts report that the *IL1B* +3954 TT genotype confers substantially elevated chronic periodontitis risk (overall pooled OR 1.60, 95% CI 1.02–2.52, for T-allele carriers vs. CC [10]). In subgroup analysis, the TT genotype conferred substantially higher risk specifically in Indian cohorts (OR 3.88, 95% CI 1.77–8.50), but not in Chinese cohorts. The pooled estimate of 1.60 should not be extrapolated to European or paediatric populations without ancestry-stratified replication. *IL1A* -889 T-allele carriage raises periodontitis odds by approximately 22% (OR 1.22, 95% CI 1.09–1.36), with the TT genotype showing a larger effect (OR 1.40, 95% CI 1.07–1.83; [24]). *IL1A* -889 is graded Moderate; *IL1B* +3954 is graded Strong on the basis of meta-analytic replication in Asian adults, although its grade in European paediatric populations is regarded as Moderate pending replication.

Pattern-recognition pathways.

At 19q13, the G allele at rs4284742 confers periodontitis risk, with effect estimate and primary GWAS attribution detailed in Section 3.3 ([19]; functional validation by [11]). The panel uses G as the risk allele following the primary GWAS attribution; investigators should verify allele orientation against GRCh38 coordinates for rs4284742 when implementing genotyping arrays. The variants rs4284742 and rs11084095 are included in the panel as the periodontal *SIGLEC5* sub-index with Strong evidence grade. Evidence for *TNFA* and *FCGR2A* polymorphisms remains inconsistent across populations; these loci are not incorporated into the panel.

Genotype-guided periodontal surveillance in paediatric populations requires prospective validation before clinical adoption. Until such evidence is available, the panel supports research-grade stratification only, with clinical decisions based on conventional risk indicators.

Other periodontitis-related loci involved in matrix remodelling, including *MMP3* and related candidate variants (e.g., [30]), were reviewed but not retained because replication remained limited or inconsistent (Supplementary Table S5).

3.6. Pain Sensitivity and Neurobehavioural Genetics

Genetic variants influencing nociception and catecholamine metabolism are relevant to paediatric dental care because they modulate pain thresholds during restorative procedures and may affect patient cooperation. The *COMT* Val158Met variant (rs4680) is the primary representative of this domain in the 22-SNP panel; its evidence base is described in Section 3.4. Three neurobehavioural variants originally considered (*HTR2A* rs6313, *ANKK1/DRD2* rs1800497, and *BDNF* rs6265) were excluded from the final panel because their supporting evidence derives exclusively from adult occupational cohorts [40–42]

without paediatric-specific replication, and no extractable odds ratio is available from any primary study in a paediatric dental context (Supplementary Table S5). Childhood parafunctional habits such as bruxism are highly prevalent, often transient, and should not be managed on the basis of genotype alone; clinical assessment and standard care pathways remain the primary determinants of intervention [43].

3.7. Craniofacial Development: Malocclusion and Agenesis

Skeletal growth and Class III malocclusion.

Mandibular prognathism shows heritability through loci governing cytoskeletal remodelling and ERK-mediated chondrogenesis. The non-conventional myosin variant *MYO1H* rs10850110 (A>G) was investigated in a candidate-gene study in an Indian population ($n = 60$; [8]), confirming the prior association reported in a Brazilian sample [27]. In Atteeri et al. [8] the reported $p < 0.0001$ is a Hardy-Weinberg equilibrium statistic rather than a case-control association, and the case-control odds ratios were non-significant; the primary quantitative support therefore rests on Cruz et al. [27], who reported OR 7.44 (95% CI 4.02–13.77), the wide confidence interval reflecting the modest cohort size and indicating winner's-curse caution. The allele may alter condylar signalling during mandibular elongation, pending replication in independent, larger, multi-ethnic cohorts. In an East Asian GWAS, a signal near *DUSP6* (a phosphatase that attenuates ERK activity) correlates with sagittal jaw discrepancy, while linkage data implicate *SPRY2*, a *DUSP6* regulator [9].

Other craniofacial growth modifiers, including *IGF1R* and *GHR*-related signals and additional endocrine-growth pathway candidates, were reviewed but not retained because replication remained limited or population-specific (Supplementary Table S5).

Panel integration.

MYO1H rs10850110 is included as a Moderate-evidence marker. *NOG* rs1348322 is retained as Weak/Tier 2: the review [9] reports it in four families with mandibular micrognathia, without a primary cohort odds ratio; regrading to Moderate awaits independent cohort replication. A separate *DUSP6*-region signal for sagittal jaw discrepancy is discussed in [9] but has no lead SNP suitable for the panel. If prospectively validated, these markers may support enhanced craniofacial monitoring; the timing and modality of orthodontic intervention should continue to follow established clinical criteria independent of genotype.

3.8. Agenesis and Dental Morphology

Tooth agenesis, particularly affecting second premolars and lateral incisors, represents one of the most prevalent congenital dental anomalies [31]. The aetiology is predominantly genetic, involving recurrent variants in key odontogenic regulators such as *WNT10A*, *PAX9*, and *AXIN2*.

WNT10A drives tooth development through the Wnt signalling pathway. Both rare loss-of-function mutations and common polymorphisms in this gene contribute to variation in tooth number and crown morphology. The rs10177996 variant has been associated with macrodontia and increased caries susceptibility, reflecting pleiotropic effects on enamel matrix integrity and cusp dimensions [1,44].

Regulation of *PAX9* expression is modulated by promoter variants, particularly rs2073247 in combination with -912C. This haplotype configuration has been associated with reduced incidence of molar and premolar agenesis, while the alternative G-1031/T-912 haplotype shows enrichment in hypodontia cohorts, suggesting a dosage-sensitive mechanism controlling early dental patterning [36].

At the *AXIN2* locus, rs2240308 has been implicated in incisor-premolar agenesis. *AXIN2* encodes a Wnt pathway antagonist involved in epithelial-mesenchymal signalling during odontogenesis. *AXIN2* variants also confer susceptibility to colorectal neoplasia,

highlighting the gene's broader developmental and oncogenic relevance and its implications for incidental findings management in paediatric genomic screening [45]. Some reports indicate a potential contribution to craniofacial growth anomalies, including skeletal Class III malocclusion.

Dental morphology variation such as shovel-shaped incisors and increased enamel thickness correlates strongly with the *EDAR* rs3827760 Val370Ala substitution, prevalent in East Asian groups and explaining a substantial proportion of variance in marginal-ridge prominence and crown proportions [34]. Within the present evidence base, *EDAR* has the clearest support for human dental morphological variation, particularly incisor shape, though its applicability is population-specific and should not be generalised beyond the ancestral groups in which the association was established.

The panel includes *WNT10A*, *PAX9*, *AXIN2*, and *EDAR* as candidate markers of agenesis and dental morphology; if prospectively validated, these loci may support earlier developmental surveillance, but orthodontic decisions should continue to rely on established clinical criteria.

3.9. Master SNP Panel Summary

Each SNP in the panel is categorised according to its primary oral-health phenotype; pleiotropic effects influencing multiple traits are noted where relevant. Evidence is graded as follows: Strong = genome-wide significant association or meta-analytic replication with appropriate multiple-testing control; Moderate = replicated in two or more independent studies with consistent direction of effect; Weak = preliminary evidence from a single study, adult-only evidence without paediatric replication, or mechanistic plausibility without population-level validation. Each association is additionally labelled by evidence provenance: paediatric (primary paediatric cohort), adult-relevant (adult or mixed-age evidence with plausible paediatric onset relevance), or exploratory (single-study or mechanistic). Provenance is indicated in the Population column of Tables 2 and S4.

The panel distinguishes two operational tiers. Tier 1 (Strong evidence, $n = 12$) comprises variants meeting genome-wide significance or meta-analytic replication thresholds; clinical validity has not been established for any variant in this tier. Tier 2 (Moderate or Weak evidence, $n = 10$) comprises variants with consistent but less extensively replicated support, designated for research-grade use pending prospective paediatric validation. Tier assignment for each variant is indicated in the Evidence grade/Tier/Study design column of Table 2. Tier 2 comprises Moderate-evidence variants together with a small number of Weak-graded variants retained only where they provide otherwise-absent trait-cluster coverage; all are flagged as research-use-only. The two-tier scheme itself did not form part of the original pre-specified protocol; it was introduced during revision to make the evidence hierarchy operational, so the retention of selected Weak-graded variants within Tier 2 is a post hoc refinement disclosed here for transparency. Weak-graded variants lacking any extractable effect estimate, or supported only by adult-only or unreplicated evidence, were excluded and are listed with rationale in Supplementary Table S5. Cross-ancestry effect-estimate and allele-frequency heterogeneity for Tier 1 variants are summarised in Table 3.

Table 2 presents the complete 22-SNP panel organised by trait cluster, reporting rsID, gene symbol, primary phenotype, key citations, evidence grade (Strong/Moderate/Weak), tier (Tier 1 = higher-evidence research-grade; Tier 2 = research-grade, pending validation), and study design. The panel provides a structured, evidence-graded genomic reference for future paediatric oral-health research; it does not constitute a validated screening tool and should not be applied clinically without prospective evaluation in independent paediatric cohorts.

Figure 2 synthesises the 22-SNP panel composition across the five trait clusters, the tier distribution of evidence strength, and the workflow from sample collection to research-grade interpretation.

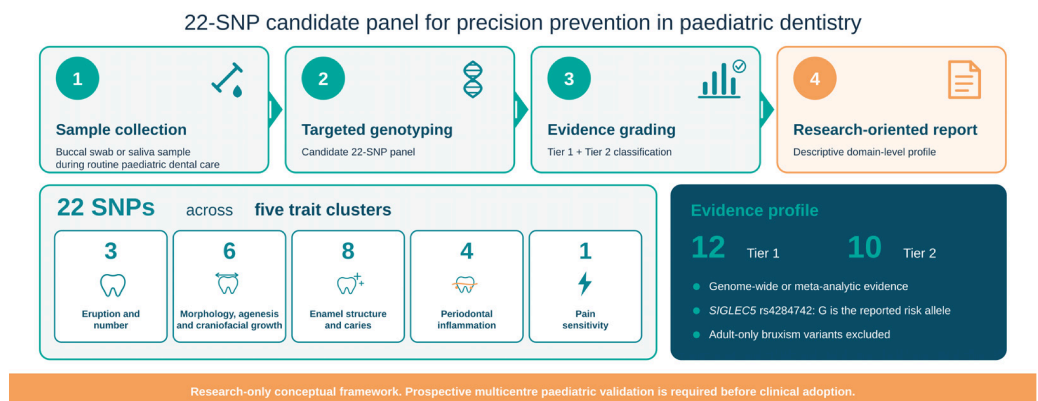


Figure 2. 22-SNP candidate panel for evidence-graded genetic risk stratification in paediatric oral health. The four-stage workflow (saliva sampling → genotyping → evidence-graded interpretation → research report) precedes a panel summary distributing the 22 variants across five trait clusters: eruption and number ($n = 3$), morphology, agenesis, and craniofacial growth ($n = 6$), enamel and caries ($n = 8$), periodontal inflammation ($n = 4$), and pain sensitivity ($n = 1$). Tier 1 designates 12 variants meeting genome-wide significance or meta-analytic replication thresholds; Tier 2 designates 10 variants with moderate or exploratory evidence pending paediatric validation. *SIGLEC5* rs4284742 risk allele is G per Munz et al. [19] GWAS attribution; functional validation by Mueller et al. [11]; three adult-cohort-only bruxism variants and one preprint-only variant were excluded from the final panel. The orange band marks research-only status; clinical adoption requires prospective multicentre paediatric validation. GWAS, genome-wide association study; SNP, single-nucleotide polymorphism.

Table 2. 22-SNP panel organised by trait cluster (Groups 1–5) with genotype-phenotype associations. The Evidence grade/Tier/Study design column reports the primary population(s) in which supporting evidence was generated where relevant. Effect estimates represent the source population cited and may not be transferable across ancestries or age groups; see Supplementary Table S4 for full population annotations. Detailed biological-function and genotype-level annotations are provided in Sections 3.1–3.8 and Supplementary Table S4.

Group 1—Tooth Eruption and Number				
rsID	Gene (Protein)	Genotype: Reported Phenotype Association *	References	Evidence Grade (Tier)/Study Design
rs7924176	<i>ADK</i> (adenosine kinase)	G/G—higher probability of slower permanent tooth eruption; A/G—intermediate; A/A—higher probability of earlier eruption †	[6]	Strong/Tier 1 GWAS
rs17101923	<i>HMGA2</i> (high mobility group AT-hook 2)	G/T—higher probability of earlier primary tooth eruption and more erupted teeth; G/G—intermediate; T/T—higher probability of later eruption and fewer erupted teeth †	[22]	Strong/Tier 1 GWAS
rs1799922	<i>CALU/OPN1SW</i> (calumenin/opsin 1 short-wave-sensitive)	T/G—higher probability of earlier eruption and more erupted teeth; T/T—intermediate; G/G—higher probability of later eruption and fewer erupted teeth †	[22]	Weak/Tier 2 GWAS (single cohort; no independent replication; no extractable OR)

Table 2. Cont.

Group 2—Tooth Morphology and Agenesis				
rsID	Gene (Protein)	Genotype: Reported Phenotype Association *	References	Evidence Grade (Tier)/Study Design
rs10177996	WNT10A (Wnt ligand)	C/C—larger crown dimensions; T/C—intermediate; T/T—smaller dimensions (derived C allele associated with larger teeth; higher frequency in Eurasians; [44])	[44]	Strong/Tier 1 GWAS + meta-analysis
rs3827760	EDAR (ectodysplasin A receptor)	C/C—pronounced shovelling; C/T—intermediate; T/T—spatulate incisors ‡	[34]	Strong/Tier 1 GWAS
rs2073247	PAX9 (paired box 9)	G/G—higher molar-premolar agenesis risk; G/A—intermediate; A/A—lower risk †	[36]	Weak/Tier 2 Candidate-gene (single Turkish cohort; haplotype effect only; no standalone OR)
rs2240308	AXIN2 (axis inhibition protein 2)	T/T—higher probability of incisor-premolar agenesis; T/C—partial; C/C—typically unaffected †	[37]	Moderate/Tier 2 Candidate-gene
rs10850110	MYO1H (myosin 1H)	G/G—higher mandibular prognathism prevalence; G/A—intermediate; A/A—reduced risk ‡ (Indian single-centre study, n = 60; OR not reported; [8])	[8]	Moderate/Tier 2 Candidate-gene
rs1348322	NOG (noggin)	rare-allele homozygosity associated with mandibular micrognathia in four families †	[9]	Weak/Tier 2 Review
Group 3—Tooth Structure and Caries Susceptibility				
rsID	Gene (Protein)	Genotype: Reported Phenotype Association *	References	Evidence Grade (Tier)/Study Design
rs12640848	ENAM (enamelin)	A/A or A/G—elevated early-childhood caries risk ([3]; OR range 2–3 across studies); note: a separate meta-analysis [14] found no significant association for this SNP alone ‡; G/G—lower risk	[3,26]	Strong/Tier 1 Meta-analysis
rs17878486	AMELX (amelogenin X)	T/T—OR approximately 1.40 for early-childhood caries across 24 cohorts ‡; T/C—intermediate; C/C—lower risk	[14]	Strong/Tier 1 Meta-analysis
rs1784418	MMP20 (enamelysin)	T/T—weaker enamel and greater caries experience; T/C—intermediate; C/C—protective trend ‡	[3]	Strong/Tier 1 Meta-analysis
rs1594318	ALLC (GWAS locus; mechanism uncharacterised)	G/G—greater caries risk; G/C—intermediate; C/C—modest protection (C allele OR 0.85, EAF 0.60; [2]) ‡	[2]	Strong/Tier 1 GWAS
rs7738851	NEDD9 (neural-crest regulator)	A/A—higher permanent-tooth caries risk (OR 1.28); A/G—intermediate; G/G—baseline	[2]	Strong/Tier 1 GWAS
rs2228570	VDR (vitamin D receptor, FokI)	T/T—over-represented in caries-active children; T/C—intermediate; C/C—more common in caries-free peers ‡	[46]	Weak/Tier 2 Candidate-gene (single Indian cohort; no independent replication; no extractable OR)

Table 2. Cont.

rs713598	TAS2R38 (bitter-taste receptor)	G/G (AVI/AVI)—non-taster, higher sugar intake and caries risk; G/C—intermediate; C/C (PAV/PAV)—taster, reduced risk §	[21,47]	Moderate/Tier 2 Meta-analysis + cross-sectional
rs2242670	KLK4 (kallikrein-4)	C/C—elevated early-childhood caries risk; C/G—intermediate; G/G—lower risk ‡	[4]	Moderate/Tier 2 Candidate-gene
Group 4—Periodontitis and Inflammatory Susceptibility				
rsID	Gene (Protein)	Genotype: Reported Phenotype Association *	References	Evidence Grade (Tier)/Study Design
rs1800587	IL1A (interleukin-1α)	T/T—higher odds of chronic periodontitis (genotype OR 1.40; T-allele OR 1.22) and greater attachment loss ‡; T/C—intermediate; C/C—lower risk	[24]	Moderate/Tier 2 Meta-analysis
rs1143634	IL1B (interleukin-1β, +3954 C>T)	T/T—overall pooled OR 1.60 (95% CI 1.02–2.52) for T-allele carriers vs. CC in 20 Asian adult case-control studies; Indian subgroup TT vs. CC OR 3.88 (95% CI 1.77–8.50); paediatric replication required ‡; T/C—intermediate; C/C—baseline risk	[10]	Strong/Tier 1 Meta-analysis (Strong in Asian adults; evidence grade in European paediatric populations is Moderate pending replication)
rs4284742	SIGLEC5 (sialic-acid-binding Ig-like lectin 5)	G/G—GWAS risk allele (OR 1.34 ‡); A/G—intermediate; A/A—minor allele, reduced MAFB binding	[11,19]	Strong/Tier 1 GWAS + functional
rs11084095	SIGLEC5 (enhancer variant)	A/A—causal allele linked to higher periodontitis risk; A/G—partial effect; G/G—normal expression †	[11]	Strong/Tier 1 GWAS + functional
Group 5—Pain Sensitivity				
rsID	Gene (Protein)	Genotype: Reported Phenotype Association *	References	Evidence Grade (Tier)/Study Design
rs4680	COMT (catechol-O-methyltransferase, Val158Met)	Met/Met (A/A)—higher pain sensitivity; Val/Met (G/A)—intermediate; Val/Val (G/G)—lower pain sensitivity ‡	[12]	Moderate/Tier 2 Candidate-gene

* Genotype-phenotype entries are simplified associations reported in the cited source population, expressed as an increased or decreased probability, and must not be read as deterministic clinical predictions. Every genotype row denotes a population-level probabilistic association in the stated source population, not an individual-level clinical prediction; phenotype labels such as ‘earlier eruption’ or ‘agenesis’ should be read as a higher or lower probability of the stated outcome. † No extractable OR/β estimate available from primary source; association signal only; see Supplementary Table S4. ‡ Effect estimate refers to the source population reported in Supplementary Table S4 and may not be transferable across ancestries or age groups. § rs713598 tags the AVI/PAV haplotype; full haplotype discrimination requires genotyping at rs713598, rs1726866, and rs10246939. Tier 1 indicates statistical replication at the GWAS or meta-analytic level and does not imply established clinical validity. Gene symbols follow HGNC convention. Population notes: EDAR rs3827760 applies primarily to East Asian populations (near-fixation); ENAM rs12640848 results are inconsistent across meta-analyses ([14]: OR 1.15, $p = 0.310$ non-significant vs. [3]: OR 2–3); IL1B rs1143634 OR 1.60 (overall) and OR 3.88 (Indian subgroup) are from Asian adult cohorts and likely overestimate risk in European paediatric populations; MYO1H rs10850110 is from a single Indian candidate-gene study ($n = 60$); VDR rs2228570 and PAX9 rs2073247 are each from single non-European cohorts without independent replication. FCER1G and TAS2R14 are emerging candidates in Supplementary Table S5, not included in the 22-SNP panel.

Table 3. Tier 1 SNP effect estimates and cross-ancestry allele-frequency heterogeneity. Odds ratios (OR) with 95% confidence intervals are shown where available against the source population. Alternate-allele minor allele frequencies (European/East Asian/African; gnomAD genomes, GRCh38) illustrate cross-ancestry variation relevant to transportability. Effect estimates are not transferable across ancestries without population-specific validation. ns, not significant; no OR, association reported without an extractable odds ratio.

rsID (Gene)	Trait Cluster	Effect Estimate (OR, 95% CI)	Source Population/Ancestry	Alt-Allele MAF EUR/EAS/AFR
rs7924176 (ADK)	Eruption and number	GWAS-significant; no OR	European multi-cohort [6]	0.44/0.02/0.10
rs17101923 (HMGA2)	Eruption and number	GWAS-significant; no OR	European children [22]	0.23/0.15/0.30
rs10177996 (WNT10A)	Morphology and agenesis	Larger crown dimensions; no OR	East Asian + European [44]	0.19/0.26/0.74
rs3827760 (EDAR)	Morphology and agenesis	~19% variance in incisor shovelling; no OR	East Asian [34]	0.007/0.89/0.01
rs12640848 (ENAM)	Enamel and caries	Conflicting: OR 2–3 [3] vs. OR 1.15 (0.88–1.52), ns [14]	Multi-ethnic	0.69/0.23/0.12
rs17878486 (AMELX)	Enamel and caries	OR 1.40 (1.02–1.93) [14]	Multi-ethnic (24 cohorts)	0.26/0.001/0.03
rs1784418 (MMP20)	Enamel and caries	~10% ECC increase [3]; OR 1.07 (0.76–1.49), ns [14]	Multi-ethnic	0.46/0.46/0.30
rs1594318 (ALLC)	Enamel and caries	C allele OR 0.85 [2]	Multi-ancestry paediatric (n = 19,003)	0.40/0.26/0.59
rs7738851 (NEDD9)	Enamel and caries	OR 1.28 [2]	Multi-ancestry paediatric	0.14/0.59/0.57
rs1143634 (IL1B)	Periodontal inflammation	Overall OR 1.60 (1.02–2.52); Indian TT OR 3.88 (1.77–8.50) [10]	Asian adult	0.23/0.02/0.13
rs4284742 (SIGLEC5)	Periodontal inflammation	OR 1.34 (1.21–1.48) [19]	German/Dutch/Turkish [11,19]	0.24/0.21/0.17
rs11084095 (SIGLEC5)	Periodontal inflammation	Causal, functionally validated; no OR [11]	German/Turkish	0.40/0.08/0.10

Minor allele frequencies from gnomAD genomes via Ensembl (GRCh38, release 116); full annotations including reference/alternate alleles and coordinates in Supplementary Table S4b. Frequencies are for the alternate allele reported by gnomAD and are shown to illustrate ancestry heterogeneity, not to assign risk direction.

4. Conceptual Translational Pathway

This section outlines a hypothetical translational pathway contextualising the clinical relevance of the evidence mapping above. It describes how the candidate 22-SNP panel could in principle be linked to paediatric dental care, subject to prospective validation and regulatory approvals outlined in Section 5. The pathway is speculative and should not be interpreted as a validated or deployable clinical protocol.

Four conceptual stages are proposed. First, a non-invasive saliva or buccal sample could be collected during routine paediatric dental care, with consent limited to oral-health-related genetic analysis. Second, the candidate panel could be assayed using an appropriate targeted genotyping platform. Third, detected variants could be interpreted at the domain level in relation to the evidence synthesised in this review, generating a descriptive risk profile across the five trait clusters. Fourth, any future reporting framework would need to remain descriptive and research-oriented unless prospective studies demonstrate that genotype-informed care improves outcomes beyond standard clinical assessment. Figure 1 summarises the four stages as a single schematic.

At the present stage, the panel can support only hypothetical domain-level clinical awareness rather than genotype-directed interventions. If prospectively validated, higher-risk signals in selected domains such as enamel integrity, periodontal susceptibil-

ity, craniofacial growth, and pain sensitivity might justify enhanced surveillance. Any genotype-guided preventive or treatment protocol would require formal evaluation against standard care in prospective paediatric cohorts before clinical adoption.

A major translational barrier is workforce readiness. Precision oral health has been described as a data-informed, risk-stratified approach integrating biological, behavioural, and environmental heterogeneity rather than replacing conventional clinical assessment with a single molecular signal [17,28]. The current education literature indicates that this workforce transition remains incomplete. In a scoping review of genomics education, Nisselle et al. [48] screened 4659 records and retained 104 studies from more than 30 countries, including 60 needs assessments and 52 education evaluations; only four studies reported long-term outcomes, indicating that evidence for durable implementation effects remains sparse. In dentistry specifically, Dudlicek et al. [49] obtained responses from 53 of 54 U.S. dental schools and found that only 8 (15%) reported a formal genetics course, while 49 of 52 (94%) had no genetics admission requirement. Korf [50] noted that there were 67 dental schools in the United States and Puerto Rico with essentially no genetics prerequisite, and argued that inadequate genetics education constrains dentists' ability to diagnose inherited conditions, assess genomic tests, and collaborate with the wider healthcare team. Any future implementation study would need to assess clinician training burden, genomic interpretive confidence, and communication competence alongside marker performance.

Equity is a second prerequisite for translation. Disease burden in paediatric oral health is shaped not only by biological susceptibility but also by access to care, socioeconomic position, and service distribution. Psoter et al. [51] analysed 3850 Arizona preschool children and found that household income and caregiver education were inversely associated with both any ECC and the maxillary-incisor pattern, while ethnicity and race were significantly associated with caries patterning; the authors concluded that global ECC definitions can mask pattern-specific social gradients. Bentley [52], reviewing California surveillance data from more than 21,000 children in kindergarten and third grade sampled from nearly 200 schools, reported that over 70% of third-graders had experienced tooth decay, over 25% had untreated decay, about 4% had pain or abscess, and roughly one-third of low-income children had untreated decay compared with about one-fifth of higher-income children. Choi et al. [53], using NHANES-informed data from 10,780 U.S. children, estimated that a 10% increase in NHSC dental workforce funding would reduce caries prevalence by 0.91 percentage points, avert 0.70 million decayed teeth, generate 150.58 thousand QALYs, and save \$211.39 million, with the greatest gains among Hispanic children and children in low-income households. Any future genomic prevention model in paediatric dentistry would need to be judged not only by predictive performance but also by accessibility, population coverage, and the possibility that implementation could reduce or widen existing inequalities.

A third requirement is ethical and regulatory governance. Paediatric genomic screening for oral-health risk raises questions extending beyond statistical validity, including scope-limited consent, the child's future right not to know, management of incidental findings, and communication of probabilistic results to parents. Farrow et al. [54] examined rare predicted loss-of-function variants in *AMELX*, *AMTN*, and *ENAM* using public resources containing approximately 145,000 exomes and genomes, identifying 95 variants in the combined dataset; they argued that next-generation sequencing could in principle support earlier diagnosis and monitoring in dental care, but emphasised the difficulty of implementing genomic testing in settings without established genetics infrastructure and the need for additional professional education. This is especially relevant where panel components carry implications beyond oral health, as with *AXIN2*-associated colorectal-neoplasia susceptibility. Any translational study would require explicit governance for data

retention, access, secondary use, and disclosure under GDPR and equivalent frameworks; paediatric implementation should not be treated as a simple extension of adult genomic medicine because assent, family communication, and incidental findings raise distinct challenges in children.

Prospective implementation would also require formal evaluation of feasibility and resource use. Spetz et al. [55] described an economic-analysis design embedded prospectively across four NIDCR-funded randomised prevention trials in children's oral health; all four incorporated incremental cost-effectiveness analysis from the planning stage, all collected training, implementation, personnel, supervision, service, supplies, and equipment costs, and two also incorporated cost-utility analyses. Any future translational programme for genomic prevention in paediatric dentistry would need to assess not only analytic and clinical performance but also delivery burden, workforce costs, and real-world affordability. The broader literature informing these translational considerations is summarised in Table 4.

Table 4. Evidence relevant to the conceptual translational pathway of the proposed paediatric oral-health candidate panel.

Domain	Reference	Study Type and Setting	Key Findings	Relevance to the Proposed Framework
Precision oral health	[28]	Conceptual/public-health framework, early childhood oral health	Proposes six building blocks for precision oral health in early childhood, including phenotype definition, proximal and distal determinants, biomarkers, workforce training, and policy investment.	Frames the candidate panel within a multilevel translational model rather than as a stand-alone clinical test.
Precision oral health	[17]	Narrative review, periodontology-focused	Defines precision oral health as a data-driven, risk-stratified approach intended to classify patients into more homogeneous subgroups.	Supports domain-level stratification while cautioning against simplistic genotype-to-treatment translation.
Genomics education	[48]	Scoping review of genomics education literature	4659 records screened; 104 studies included from more than 30 countries; 60 needs assessments; 52 evaluations; only 4 studies reported long-term outcomes.	Indicates that workforce education and implementation evaluation remain underdeveloped.
Dental genetics education	[49]	National survey of U.S. dental schools	53/54 schools responded; 8/53 (15%) reported a formal genetics course; 49/52 (94%) had no genetics admission requirement; 32/52 (62%) perceived a need; 45/51 (88%) wanted educational materials.	Quantifies the historical deficit in genetics training relevant to dental implementation.
Dental curricula and genomics	[50]	Invited commentary on dental curricula	Notes 67 dental schools in the United States and Puerto Rico; genetics prerequisites essentially absent; argues limited genomics teaching constrains diagnosis, test evaluation, and interprofessional collaboration.	Reinforces curricular readiness as a precondition for future translation.
Genomic integration in dental care	[54]	Database-based exploratory study and translational discussion	Used public resources containing approximately 145,000 exomes/genomes; identified 95 rare predicted loss-of-function variants across <i>AMELX</i> , <i>AMTN</i> , and <i>ENAM</i> ; discusses earlier diagnosis as a theoretical benefit but highlights implementation barriers.	Supports cautious discussion of sequencing, consent, and the limits of current clinical integration.
Oral-health disparities	[51]	Cross-sectional analysis of Arizona preschool children	3850 children analysed; income and caregiver education inversely associated with any ECC and maxillary-incisor pattern; race/ethnicity associated with caries patterning; global ECC measures may obscure subgroup-specific risk structures.	Shows that paediatric oral-disease risk is socially patterned, directly relevant to equitable genomic prevention modelling.
Oral-health disparities	[52]	Narrative disparities review using California statewide surveillance data	Among more than 21,000 children in kindergarten and third grade from nearly 200 schools: over 70% of third-graders had experienced decay; over 25% had untreated decay; about 4% had pain or abscess; low-income children had substantially more untreated disease than higher-income children.	Supports the need to evaluate structural access barriers alongside genomic risk.

Table 4. *Cont.*

Domain	Reference	Study Type and Setting	Key Findings	Relevance to the Proposed Framework
Access and underserved populations	[53]	Cost-effectiveness modelling using NHANES-linked data	10,780 U.S. children; a 10% NHSC funding increase estimated to reduce caries prevalence by 0.91 percentage points, avert 0.70 million decayed teeth, generate 150.58 thousand QALYs, and save \$211.39 million; largest gains in Hispanic and low-income children.	Shows that delivery-system investment produces measurable gains; implementation equity must be considered alongside genomic innovation.
Economic evaluation	[55]	Methods/perspective paper on economic-analysis design embedded in prevention trials	Four NIDCR-funded randomised prevention trials; all incorporated incremental cost-effectiveness analysis prospectively; all collected training, implementation, personnel, supervision, service, supplies, and equipment costs; two additionally conducted cost-utility analyses.	Supports prospective economic evaluation as an essential component of any future genomic implementation study.

The studies in Table 4 support interpreting the candidate panel as a conceptual translational framework linking evidence synthesis with workforce preparedness, social patterning of disease, ethical governance, and prospective implementation evaluation, rather than as a clinically validated genomic prevention pathway.

5. Discussion

A critical limitation of the present work is the absence of modelled or empirical clinical validity estimates (sensitivity, specificity, positive predictive value, and area under the receiver operating characteristic curve) for the 22-SNP panel as a whole. Individual effect sizes (reported in Supplementary Table S4) are modest for most variants (median OR $\approx$ 1.3–1.4 for Tier 1 caries and periodontitis SNPs), and polygenic risk scores constructed from such variants typically show limited discriminative ability when transported out of discovery cohorts [56,57]. The 8-SNP logistic-regression and neural-network models reported by Zaorska et al. [26] (AUC = 0.970 in $n = 95$, validation accuracy 73.6–87.2%) cannot be used to validate the present 22-SNP panel. Prospective studies providing ancestry-stratified, age-specific AUC estimates in independent paediatric cohorts are an explicit prerequisite before clinical implementation can be recommended.

Additional methodological limitations include the absence of inter-rater reliability statistics (Cohen's κ) for the two screening stages. Retrospective calculation was not feasible as screening decisions were not digitally logged. Future implementations of this mapping methodology should prospectively record and report κ values at both abstract-screening and full-text eligibility stages, as recommended by PRISMA 2020. For the same reason, the Q-Genie appraisal is reported at the level of total study scores and grades only; item-level domain scores were not tabulated, which limits granular inspection of specific risk-of-bias dimensions. The systematic review protocol was not registered in PROSPERO, prospectively or retrospectively. All eligibility criteria and grading rules were pre-specified and are reported without deviation in Supplementary File S1; the absence of any registration means that post hoc outcome selection cannot be formally excluded, and this should be considered when interpreting the panel composition.

Genetic association evidence for paediatric oral phenotypes has grown sufficiently to support the construction of a reproducible, evidence-graded candidate panel. Large-scale GWASs and meta-analyses have linked common and rare variants to enamel integrity, caries susceptibility, tooth eruption timing, craniofacial growth, periodontal inflammatory response, and neurobehavioural traits; replicated associations are now available across all seven originally screened domains (six after bruxism exclusion; consolidated into five panel clusters).

A fundamental limitation of the present approach is that all conditions addressed (dental caries, periodontal disease, tooth agenesis, malocclusion, and pain sensitivity) are multifactorial in origin. Genetic variants account for only a portion of phenotypic variance; dietary exposures, oral hygiene behaviour, fluoride availability, socioeconomic conditions, and early microbial colonisation each contribute substantially to individual risk [1,2,39]. A panel of 22 common SNPs with modest individual effect sizes (median OR $\approx$ 1.3–1.4 for Tier 1 caries and periodontitis variants) can be expected to capture only a limited fraction of susceptibility, and genotype-based risk stratification will be most informative when integrated with established clinical risk indicators rather than used as a standalone prediction tool. This inherent constraint of common-variant genetic panels in multifactorial disease settings must be communicated clearly to clinicians and families if the panel is ever deployed in practice.

Ancestral representation is uneven. Discovery cohorts are dominated by European and East Asian samples, so transportability to other populations needs confirmation [16,21].

Outcome definitions lack uniformity. Caries metrics range from dmft indices to ICDAS scores, and bruxism assessments vary from parental questionnaires to polysomnography, complicating effect size comparison [40].

Analytic validity and clinical utility remain insufficiently established for this panel. Evidence from similar multigene panels in other clinical domains indicates generally poor discriminative ability outside the development cohort [56,57], and no meta-analysis or replication study has yet assessed the SNP panel against independent paediatric datasets [58,59]. Rare variants and copy-number variation in enamel and agenesis genes, which may contribute additional risk not captured by common SNPs, fall outside the scope of this panel [54]. Provider readiness and genomic health literacy constitute additional translational barriers [48]: surveys indicate that most paediatric dentists lack formal genomics training and fewer than half of dental schools include genetics in their curricula [49,50]. Bridging this gap will require standardised education programmes and cost-effectiveness evidence from prospective trials before genotype-guided protocols can be justified at scale [32,55].

One variant in the panel raises a specific incidental findings concern that warrants substantive discussion rather than parenthetical acknowledgement. *AXIN2* rs2240308, included as a Moderate-evidence candidate for incisor-premolar agenesis, is also associated with an autosomal dominant predisposition to colorectal polyposis and adenocarcinoma [45]. Genotyping *AXIN2* rs2240308 in a preschool child for dental-agenesis surveillance could therefore generate a finding with significant oncological implications for the child and family, extending well beyond the intended oral-health scope. Current guidelines from the American College of Medical Genetics and Genomics (ACMG) advise against reporting unsolicited secondary findings from targeted panels unless the finding is in a medically actionable gene on the ACMG SF list and the testing laboratory has explicit secondary-findings policies in place [60]. *AXIN2* is not currently on the ACMG SF v3.2 list, but its colorectal cancer association meets the general criterion of medical actionability through colonoscopic surveillance. Any future implementation study including *AXIN2* rs2240308 must therefore: (i) obtain explicit scope-limited consent disclosing the potential for colorectal-polyposis findings; (ii) specify in advance whether secondary findings will be reported, to whom, and under what governance; (iii) ensure access to genetic counselling before and after disclosure; and (iv) address the child's developing autonomy and future right not to know. These requirements should be addressed in the ethics approval protocol before any translational study commences, and should not be treated as a simple extension of standard paediatric dental consent.

A scope-limited consent framework should be fixed before any paediatric application. At minimum it should state: (i) that genotyping is restricted to oral-health-associated variants; (ii) how the *AXIN2* rs2240308 colorectal-neoplasia association will be handled, including whether this secondary finding will be reported and to whom; (iii) parental consent together with age-appropriate child assent; (iv) data retention, access, and secondary-use rules under GDPR and equivalent frameworks; (v) the child's future right not to know and a re-contact pathway at the age of majority; and (vi) access to genetic counselling before and after any disclosure. These elements belong in the ethics protocol and should not be adapted from standard paediatric dental consent.

Addressing these gaps through prospective, multi-ethnic studies with harmonised phenotyping will sharpen risk estimates and determine whether the panel has clinical utility in paediatric dentistry.

Emerging candidates for future inclusion.

Two loci identified in the post-2020 literature do not yet meet the inclusion criteria for the 22-SNP panel but warrant monitoring as the evidence base matures. They are listed in Supplementary Table S5 as candidates for future inclusion.

FCER1G encodes the gamma subunit of the high-affinity IgE receptor and has a well-characterised role in mucosal innate immune signalling. A GWAS meta-analysis in 1306 European cases of severe periodontitis (stage III/IV grade C) with onset ≤ 35 years identified a genome-wide significant association at this locus ($p = 1.0 \times 10^{-9}$), independently of the existing *SIGLEC5* signal [25]. The biological rationale (immune dysregulation of the gingival barrier) is directly relevant to the periodontal domain of the SNP panel. At present, the absence of paediatric-specific or primary dentition replication means *FCER1G* does not meet the Moderate evidence threshold; the association is classified here as Weak/Tier 2 pending paediatric cohort replication.

TAS2R14 encodes a bitter-taste receptor that activates innate immune defence against cariogenic bacteria including *Streptococcus mutans* through the production of antimicrobial peptides and defensins at the oral epithelium. This mechanism is distinct from the sugar-preference pathway through which *TAS2R38* (already in the panel) influences caries risk. A transcriptome-wide association study meta-analysing five paediatric cohorts of children aged up to five years (total $n = 2974$) identified *TAS2R14* as a transcriptome-wide significant gene ($p < 3.09 \times 10^{-6}$), with suggestive SNP-level association [61]. Standalone SNP-level genome-wide significance has not yet been reported; *TAS2R14* is therefore classified here as Weak/Tier 2 pending a replicated SNP-level association in an independent paediatric cohort.

Priorities for validation.

Several methodological priorities should guide future work. Longitudinal, multi-ethnic birth cohorts collecting serial biospecimens with harmonised clinical end points are needed to generate generalisable risk estimates. Prospective trials comparing genotype-guided protocols-such as intensified fluoride varnish application in *ENAM* A/A carriers-with current guideline-based care would provide direct evidence of clinical benefit. Polygenic risk models require further refinement through the incorporation of gene-environment interactions, with particular attention to dietary sugar load and fluoride exposure as modifiable variables. Finally, implementation science studies examining workflow feasibility, family acceptability, and data privacy safeguards are essential before wide-scale deployment can be considered.

Future directions.

Advances in sequencing technology, federated learning architectures, and FHIR interoperability now make dynamic updating of genomic risk scores within electronic dental records technically feasible. Further integration of genomic data with salivary micro-

biomics and behavioural metrics may substantially enhance risk stratification beyond what SNP data alone can achieve. Equitable access remains a central concern: public health frameworks and reimbursement pathways must prioritise high-risk, underserved children to ensure that precision prevention narrows rather than widens existing oral-health disparities [33,51,53,62,63].

6. Conclusions

The 22-SNP panel represents a reproducible, evidence-graded candidate framework for genetic risk-stratification research in paediatric dentistry, not a validated clinical screening instrument. The panel consolidates genome-wide and meta-analytically replicated associations across five trait clusters into a transparent, tiered structure, providing a systematic starting point for future prospective validation studies. Prospective trials in independent, multi-ethnic paediatric cohorts are required to establish analytic validity, clinical utility, and cost-effectiveness before any genotype-guided preventive intervention can be adopted.

If prospectively validated, a compact, cost-controlled SNP panel could in principle support equitable access to genomic risk information across clinic settings, including in underserved populations where disease burden is highest [51,53]. Realising this potential will require not only rigorous evidence of clinical benefit but also workforce training, ethical governance frameworks, and reimbursement pathways aligned with preventive practice.

Three directions stand out for future work. Prospective multi-ethnic trials are needed to quantify absolute risk reduction and establish cost-effectiveness. Next-generation panels should incorporate salivary microbiomics, behavioural metrics, and broader polygenic scores to sharpen prediction across heterogeneous environments. Policy frameworks must align reimbursement incentives with preventive genomics or existing disparities will widen.

With rigorous validation and thoughtful implementation, genotype-guided prevention can move paediatric dentistry beyond one-size-fits-all protocols toward a model in which every child receives prevention calibrated to individual biology, lifestyle, and developmental stage.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/app16147138/s1>: File S1: Pre-specified protocol (Sections S1.1–S1.7); Figure S1: PRISMA 2020 flow diagram; Table S1: Full database search strategies; Table S2: Pre-specified exclusion categories (mapping); Table S3: Initial candidate SNP list; Table S4: Variant annotations and effect estimates for the retained panel; Table S4b: Genomic annotations for the 22 retained SNPs; Table S4c: Q-Genie quality scores for candidate-gene studies; Table S4d: HuGENet certainty assessment for GWAS and meta-analysis-derived SNPs; Table S5: Rejected variants with rationale; Table S6: Characteristics of included studies.

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Abbreviations

AUC	Area under the receiver operating characteristic curve
DMFT	Decayed, Missing and Filled Teeth index
DNA	Deoxyribonucleic acid
EFPP	European Federation of Periodontology
EHR	Electronic Health Record
FHIR	Fast Healthcare Interoperability Resources
GDPR	General Data Protection Regulation
GWAS	Genome-wide association study
ICDAS	International Caries Detection and Assessment System
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRS	Polygenic risk score
QC	Quality control
SNP	Single-nucleotide polymorphism
TMD	Temporomandibular disorder

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