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SYSTEMATIC REVIEW

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Association between genetic polymorphisms and dental age variation: a systematic review

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Abstract

Background: The study aimed to perform a systematic review to elucidate the scientific evidence supporting the association between genetic polymorphisms and variation in dental age. **Methods**: A comprehensive search was conducted in PubMed, Scopus, Web of Science, Embase, Virtual Health Library, and other sources. Observational studies assessing the association between genetic polymorphisms and dental age variation were included. Study quality was assessed using the Q-Genie tool. Data from primary studies were synthesized narratively and statistically. The certainty of evidence was evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. **Results**: From the initial search, five studies with sample sizes ranging from 37 to 177 participants (total n = 472), met the inclusion criteria. All studies were of good quality and used Demirjian's method to assess dental age. In total, 31 polymorphisms across 19 candidate genes were analyzed. Only two genetic polymorphisms were associated with dental age variation: Fibroblast Growth Factor (*FGF18* rs4073716) and Transforming Growth Factor, Beta-1 (*TGFB1* rs4803455). The certainty of evidence was very low for all outcomes evaluated. **Conclusions**: Based on the current evidence, there is no consistent or reliable association between genetic polymorphisms and dental age variation. Although two specific polymorphisms were associated with dental age variation in individual studies, the very low certainty of evidence prevents drawing definitive conclusions. Further robust and well-designed studies are needed to clarify this potential association. **The PROSPERO Registration**: The review was registered in International Prospective Register of Systematic Reviews (PROSPERO) and the registration number CRD420251041224 was assigned to it.

Keywords

Genetic polymorphisms; Age determination by teeth; Dental development; Dental age; Systematic review

1. Introduction

Tooth development is a complex and continuous biological process that occurs in conjunction with key phases of a child's growth and maturation [1, 2]. This process has important applications across several fields. In clinical practice, understanding dental development can support diagnostic accuracy, inform therapeutic decisions, and guide treatment planning, particularly in areas such as orthodontics and pediatric dentistry [2–4]. In forensic contexts [5] and anthropological studies [6], understanding dental growth patterns is essential, particularly in cases involving clandestine migration, child sexual abuse, and the identification of unknown individuals [7].

A common method used in several studies to estimate chronological age involves analyzing the progression of dental development [8, 9]. However, it is important to recognize that individuals of the same chronological age may differ significantly in their dental development stages. Therefore, biological markers of development, particularly dental maturation, may provide a more accurate representation of an individual's developmental status than chronological age [10].

Many aspects may be involved in the individual variation of dental age. Several factors play an important role in tooth development, such as local, environmental, and systemic factors, including hormones and genetic influences. Variations in genes involved in these pathways may influence the timing of dental maturation, contributing to interindividual differences in dental age beyond environmental influences. This biological framework provides mechanistic plausibility for investigating

genetic polymorphisms as determinants of variation in dental age [11–13].

Recent studies investigating single nucleotide polymorphisms (SNPs) in the context of oral diseases have highlighted their potential as biomarkers for identifying individuals at greater risk and for guiding personalized treatment strategies. Systematic reviews in dental genetics have identified strong associations between specific genetic polymorphisms and a range of oral health conditions. Among these, SNPs have been shown to play a critical role in the etiology of dental anomalies, such as enamel defects, dental fluorosis, and caries [14, 15]. Additionally, while a systematic review has already established a relationship between dental age and malocclusion [16], there remains a need for scientific evidence regarding the influence of genetic polymorphisms on variations in dental age. In this context, this systematic review aims to elucidate the scientific evidence supporting the association between genetic polymorphisms and variation in dental age.

2. Methods

2.1 Focused question

This systematic review seeks to answer the following research question: Does the presence of specific genetic polymorphisms influence the variation of dental age in children and adolescents undergoing dental development?

2.2 Registration and protocol

This study was registered in the PROSPERO database (https://www.crd.york.ac.uk/prospero/) under the identification number CRD420251041224. It followed the Cochrane collaboration guide [17] and was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Supplementary material 1**) [18].

2.3 Eligibility criteria

A PEOs framework (*i.e.*, Population, Exposure, Outcome, Study design) was used to structure the search strategy, devise the review question and related search terms.

The eligibility criteria (inclusion) was outlined according to the acronym PEOs:

Population (P): Children and adolescents undergoing dental development.

Exposure (E): Presence of specific genetic polymorphisms (single nucleotide polymorphisms or other variants) in genes potentially involved in craniofacial and dental development.

Outcome (O): Dental age, dental age variation, or timing of dental maturation assessed using validated dental age estimation methods.

Study design (S): Observational cross-sectional genetic association studies.

Case reports, systematic reviews, book chapters, guidelines, studies evaluating parents and siblings, and animal and *in vitro* studies were excluded.

2.4 Information sources and search strategy

The literature search was performed on Medline via PubMed, Web of Science, Virtual Health Library (VHL), LILACS (Literatura Latino-americana e do Caribe em ciências da saúde) literature, Embase and Scopus databases. The search strategy combined MeSH terms (Medical Subject Headings) for PubMed, Descriptors for Health Sciences (DECS) for VHL, and Emtree terms (Embase Subject Headings) for Embase database. Free terms with the use of Boolean operators (OR, AND) were also used and included synonyms related to the main outcomes (dental age and genetic polymorphisms). Additional searches were performed in other sources, including Google Scholar (https://scholar.google.com.br/). References of the included studies were manually checked for further relevant publications, and experts in the field, identified through ExpertScape (https://www.expertscape.com/), were contacted via email and social media (https://www.researchgate.net/). All searches were conducted on the same day and updated through August 2025, with alerts activated in the databases. Detailed search strategies for each database are provided in **Supplementary Table 1**. No restrictions on language or publication date were applied, and the initial strategy was structured using terms equivalent to the research question.

2.5 Selection process

The retrieved articles were exported to the reference management software Mendeley for automatic detection and manual deletion of duplicates, enabling the selection process to proceed. To identify potentially eligible articles, titles and abstracts were initially reviewed. Then, the studies initially included were read in full, with eligibility criteria strictly applied for the final selection of articles. The entire process was conducted independently by two reviewers (LAA and ECT). A consensus was reached after discussion in every discrepancy between the examiners. To evaluate the agreement between the authors, 10% of the publications were selected randomly in the research carried out, having their classification compared and then the Kappa statistical index was determined (0.80). When, in this process, there was any disagreement of opinions, a third reviewer (LSA) was consulted to resolve the disagreement. When the title and abstract were not clear, the articles were read in full and reapplied the eligibility criteria as previously described.

2.6 Data collection process and data items

The relevant data was extracted by two reviewers independently (LAA and ECT) and presented in detail grouped by year of publication. Doubts were solved in consensus meeting with a third author (LSA). The data from the included studies were compiled and organized according to sample characterization of selected studies, and description of the investigated genetic polymorphisms. For each included study, we extracted information regarding validation of the dental age assessment method within the study population.

During the selection and extraction of data, contact with the authors was established via email in case of missing or unclear

information, doubts, or lack of information. If the contacted authors did not provide the requested data or failed to respond to the email within 40 days, the study was included only in the qualitative analysis.

2.7 Study quality assessment

The Q-Genie tool, developed and validated by McMaster University, is used to rate the quality of genetic association studies [19, 20]. The quality of the included studies was independently assessed by two authors (LAA and LMNN) using this tool. Any disagreements were resolved by consensus or by consulting another author (LSA). The Q-Genie tool includes 11 assessment areas, such as rationale, outcome classification, comparison groups, exposure, source of bias, power analysis, statistical methods, test of assumptions, inferences, and conclusion. It is a Likert-type scale with 11 questions; each scored from 1 to 7 (Fig. 1, Ref. [19]). For studies with a control group, a score <35 indicates poor quality, >35 but <45 indicates moderate quality, and >45 indicates good quality. For studies without a control group, a score <32 indicates low quality, >32 but <40 indicates moderate quality, and >40 indicates good quality.

2.8 Certainty assessment

Two reviewers (LAA and LSA) independently analyzed these evaluations. The quality of the evidence (certainty in the estimates of effect) was determined for the out-come using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. From each outcome evaluated, the certainty of the evidence using the GRADE approach was made. It was checked if there are serious or very serious issues, related to risk of bias, inconsistency, indirectness, imprecision, and publication bias. GRADE defines the certainty of scientific evidence more clearly and objectively, and can be classified as high, moderate, low, or very low [21].

3. Results

3.1 Study selection

The systematic search identified 1069 records from electronic databases (PubMed, Web of Science, Embase, Scopus, and the Virtual Health Library) and 100 additional records from other sources, including Google Scholar and citation searching. After removing 274 duplicates and 16 records for other reasons, 779 unique records were screened. Of these, 769 were excluded based on title and abstract, and 10 reports were retrieved for full-text evaluation. Following assessment, 5 articles met the eligibility criteria from database searches and incorporated into the systematic review. The complete selection process is detailed in Fig. 2.

3.2 Study characteristics and results of individual studies

A total of five studies [22–26] were identified, including 472 participants, that investigated the association between genetic polymorphisms and variations in dental age, as summarized in Table 1 (Ref. [22–26]). These studies were published between 2019 and 2025 and conducted predominantly in Brazil [23–26]. Sample sizes ranged from 37 to 177 participants, with age groups varying from early childhood to adolescence. All investigations applied the Demirjian method (1973) [27] for dental age estimation, either alone or in combination with other approaches.

In total, 31 polymorphisms across 19 candidate genes were analyzed. A wide range of genetic variants was analyzed, encompassing genes related to growth factors *FGFR* (Fibroblast Growth Factor Receptor), *FGF* (Fibroblast Growth Factor), *IGF2R* (Insulin-Like Growth Factor 2 Receptor), *TGFB1* (Transforming Growth Factor Beta 1), *TGFBR2* (Transforming Growth Factor Beta Receptor 2), vitamin D metabolism and signaling *VDR* (Vitamin D Receptor), *CYP27B1* (Cytochrome P450 Family 27 Subfamily B Member 1), *CYP24A1* (Cytochrome P450 Family 24 Subfamily A Member 1), and other regulatory pathways, including *EGFR* (Epidermal Growth Factor Receptor), *ESR1* (Estrogen Receptor 1), and *ESR2* (Estrogen Receptor 2). Despite this diversity, most studies reported no significant associations between genetic polymorphisms and dental age. Notable exceptions included *FGF18* rs4073716, which was associated with advanced dental age relative to chronological age in U.S. children [22] and *TGFB1* rs4803455, associated with dental age in Brazilian children without cleft lip and/or palate [26] (Table 2, Ref. [22–26]).

3.3 Risk of bias in studies

The five included studies scored between 62 and 68 on the Q-Genie quality assessment tool, and all were classified as having good methodological quality (Table 3, Ref. [22–26]). The most common methodological limitations were related to four key areas: inadequate disclosure and discussion of potential sources of bias, insufficient description and testing of underlying assumptions, weak justification of inferences, and lack of evidence that the study was adequately powered. In contrast, all studies scored highly (7/7) on critical elements such as clarity of hypothesis, outcome classification, group descriptions, and statistical methodology, reflecting strong

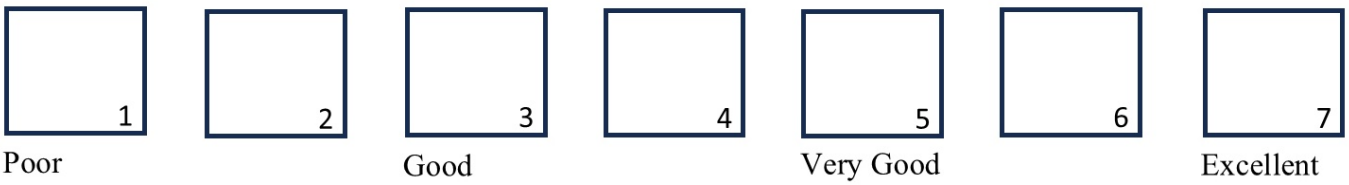

FIGURE 1. Likert scale with 11 questions; each scored from 1 to 7 used in the Q-Genie tool assessed in [19].

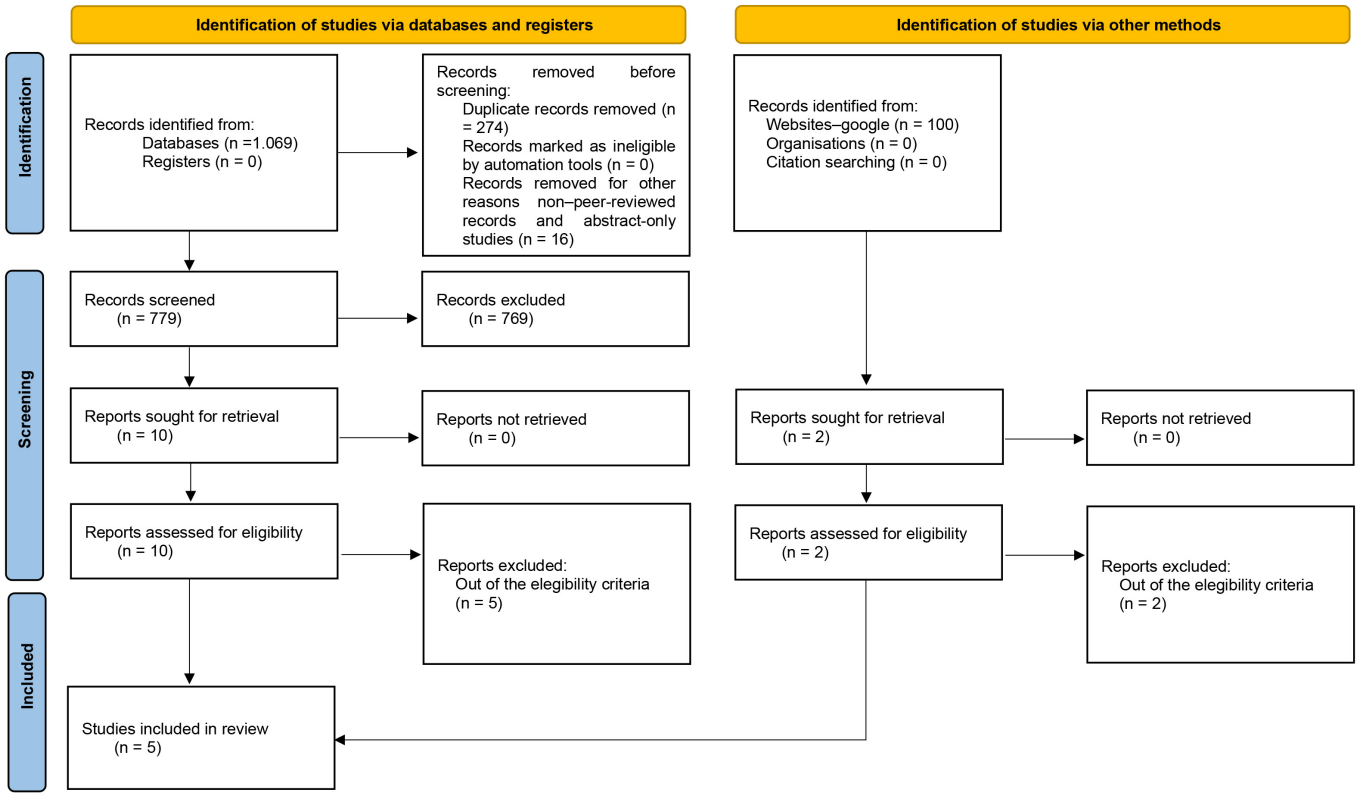

FIGURE 2. Flowchart considering studies/reports identification, screening and included.

design and reporting practices in these areas. Fonseca-Souza *et al.* [26] (2025) was the only study that reported adequate sample sizes and statistical power, contributing to their relatively higher overall Q-Genie scores (68).

3.4 Certainty of evidence

The quality of evidence for the association between genetic polymorphisms and dental age variation was presented in Table 4. Overall, all outcomes were rated as very low certainty. This classification was primarily due to serious risk of bias, related to the lack of clear inclusion and exclusion criteria, small sample sizes, and limited methodological detail. In addition, many outcomes presented very serious inconsistency, largely driven by heterogeneity in age ranges and conflicting directions of effect across studies. Imprecision was also frequently identified, particularly due to studies not meeting the optimal sample size threshold (n $\geq$400). No study met criteria for higher levels of certainty, and no upgrading factors were applicable.

4. Discussion

This systematic review identified a limited number of studies reporting statistically significant associations between specific genetic polymorphisms and dental age variation. Among the seven studies included, only two demonstrated such associations. Modesto *et al.* [22] (2019), in a U.S.-based population, reported a significant link between the *FGF18* rs4073716 variant and the evaluated outcome. Fonseca-Souza *et al.* [26] (2025) identified a significant association with *TGFB1* rs4803455. The remaining studies did not report statistically significant findings. These results reflect the complexity of genetic contributions to dental maturation and indicate that current evidence remains limited and inconsistent.

The diversity of genetic variants investigated highlights the complexity of the biological pathways potentially involved in dental development. Genes related to growth factors (*FGFR*, *FGF*, *IGF2R*, *TGFB1*, and *TGFBR2*) play critical roles in cellular proliferation, differentiation, and tissue development, which are fundamental processes in dental maturation. Similarly, genes involved in vitamin D metabolism and signalin (*VDR*, *CYP27B1*, *CYP24A1*) are essential regulators of calcium homeostasis and bone metabolism, which may impact tooth development and mineralization. Additionally, other regulatory genes, such as *EGFR*, *ESR1*, and *ESR2*, are implicated in hormonal signaling, protein transport, and receptor activity, all of which could modulate dental tissue formation. Despite this biological plausibility, most studies did not observe statistically significant associations, reinforcing the multifactorial and polygenic nature of dental development.

Evidence from twin studies provides a biological framework for interpreting this variability. Even monozygotic twins may exhibit differences in dental traits, reflecting environmental exposures, epigenetic regulation, and stochastic developmental influences. This variability does not contradict genetic contributions, but suggests that individual variants likely exert modest effects within a complex biological system. Such context helps explain small effect sizes, the need for large samples, and inconsistencies across populations.

TABLE 1. General characteristics of the included studies.

Author/Year	Population/ Ethnicity	Age (yr)	N (♂/♀)	Method for dental age estimation	Reference to validation of dental age assessment method	Variables analyzed	Main findings on the association between genetic polymorphisms and dental age variation
Modesto *et al.* [22], 2019	USA	2–6 (DA), 2–20 (skeletal maturation)	177 (82♂/95♀)	Demirjian (1973)	No	DA × sex, ASA, BMI; DA × polymorphisms (*FGFR1*, *FGFR2*, *IGF2R*, *FGF3*, *FGF7*, *FGF10*, *FGF13*, *FGF18*); Skeletal maturation × BMI	FGF18 rs4073716: excess of heterozygotes in children with DA > chronological age (p = 0.04).
Küchler *et al.* [23], 2022	Brazil	10–16	37 (17♂/20♀)	Demirjian (1973); Hofmann (2017)	No	DA × *VDR* polymorphisms; Vitamin D levels	No significant association ($p >$ 0.05).
Madalena *et al.* [24], 2023	Brazil	7–16	79 (35♂/44♀)	Demirjian (1973)	No	DA × polymorphisms (*ESR1*, *ESR2*)	No significant association ($p >$ 0.05).
Madalena *et al.* [25], 2025	Brazil	7–16	79 (35♂/44♀)	Demirjian (1973)	No	DA × polymorphisms (*PTH*, *VDR*, *CYP27B1*, *CYP24A1*)	No significant association ($p >$ 0.05).
Fonseca-Souza *et al.* [26], 2025	Brazil	5–14	100 CL ± P (61♂/39♀), 109 controls (52♂/57♀)	Demirjian (1973)	No	DA × CL ± P; DA × polymorphisms (*EGF*, *EGFR*, *TGFB1*, *TGFBR2*)	TGFB1 rs4803455 associated with DA variation in children without CL ± P ($p < 0.01$).

DA: Dental Age; ASA: Asthma; BMI: Body Mass Index; FGFR: Fibroblast Growth Factor Receptor; IGF2R: Insulin-Like Growth Factor 2 Receptor; FGF: Fibroblast Growth Factor; VDR: Vitamin D Receptor; ESR1/ESR2: Estrogen Receptor 1/2; PTH: Parathyroid Hormone; CYP27B1: Cytochrome P450 Family 27 Subfamily B Member 1; CYP24A1: Cytochrome P450 Family 24 Subfamily A Member 1; CL ± P: Cleft Lip with or without Palate; EGF: Epidermal Growth Factor; EGFR: Epidermal Growth Factor Receptor; TGFB1: Transforming Growth Factor Beta 1; TGFBR2: Transforming Growth Factor Beta Receptor 2; ♂: Male; ♀: Female.

TABLE 2. Description of the selected studies—genetic polymorphism.

Author, Year	Genes Studied	Polymorphisms Evaluated	Genes/SNPs Analyzed	Significant Association
Modesto *et al.* [22], 2019	8	13	F*GFR1* (rs13317); *FGFR2* (rs2981582, rs1219648); *IGF2R* (rs2282141, rs2065396); *FGF3* (rs4980700, rs1893047); *FGF7* (rs2413958); *FGF10* (rs1011814, rs1448037); *FGF13* (rs10856566, rs12838463); *FGF18* (rs4073716)	*FGF18* rs4073716
Küchler *et al.* [23], 2022	1	2	*VDR* (rs739837-BglI, rs2228570-FokI)	-
Madalena *et al.* [24], 2023	2	4	*ESR1* (rs9340799, rs2234693); *ESR2* (rs1256049, rs4986938)	-
Madalena *et al.* [25], 2025	4	6	*PTH* (rs694, rs6256, rs3072470); *VDR* (rs7975232 ApaI); *CYP27B1* (rs4646536); *CYP24A1* (rs927650)	-
Fonseca-Souza *et al.* [26], 2025	4	6	*EGF* (rs4444903, rs2237051); *EGFR* (rs2227983); *TGFB1* (rs1800470, rs4803455); *TGFBR2* (rs3087465)	*TGFB1* rs4803455

FGFR1/2: Fibroblast Growth Factor Receptor 1/2; IGF2R: Insulin-Like Growth Factor 2 Receptor; FGF3/7/10/13/18: Fibroblast Growth Factor 3, 7, 10, 13, 18; VDR: Vitamin D Receptor; ESR1/2: Estrogen Receptor 1/2; PTH: Parathyroid Hormone; CYP27B1: Cytochrome P450 Family 27 Subfamily B Member 1; CYP24A1: Cytochrome P450 Family 24 Subfamily A Member 1; EGF: Epidermal Growth Factor; EGFR: Epidermal Growth Factor Receptor; TGFB1: Transforming Growth Factor Beta 1; TGFBR2: Transforming Growth Factor Beta Receptor 2; SNPs: single nucleotide polymorphisms.

TABLE 3. Quality assessment of the included studies.

Criteria	Modesto *et al.* [22], 2019	Küchler *et al.* [23], 2022	Madalena *et al.* [24], 2023	Madalena *et al.* [25], 2025	Fonseca-Souza *et al.* [26], 2025
Adequacy of the presented hypothesis and rationale	7	7	7	7	7
Classification of the outcome	7	7	7	7	7
Description of comparison groups	7	7	7	7	7
Technical classification of the exposure	7	7	7	7	7
Non-technical classification of the exposure	7	7	7	7	7
Disclosure and discussion of sources of bias	3	3	3	3	3
Study adequately powered	3	3	3	3	7
Description of planned analyses	7	7	7	7	7
Statistical methods	7	7	7	7	7
Description and test of all assumptions and inferences	3	3	3	3	3
Conclusions drawn by the authors were supported by the results and appropriate methods	6	4	6	6	6
Overall score	64	62	64	64	68
*Quality of the study	Good	Good	Good	Good	Good

**Cut-off: <32 = Low; 32–40 = Moderate; >40 = Good. Studies with control groups: <35 = Poor; 35–45 = Moderate; >45 = Good.*

TABLE 4. Quality of evidence assessment using GRADE—outcomes considering genes and SNPs.

Outcome	No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty of Evidence
FGFR1 (rs13317); *FGFR2* (rs2981582, rs1219648); *IGF2R* (rs2282141, rs2065396); *FGF3* (rs4980700, rs1893047); *FGF7* (rs2413958); *FGF10* (rs1011814, rs1448037); *FGF13* (rs10856566, rs12838463); *FGF18* (rs4073716)	1	Observational	Serious[a]	Very serious[b]	Not serious	Not serious	None	⊕◯◯◯ Very Low
VDR (rs739837-BglI)	1	Observational	Serious[a]	Very serious[b]	Not serious	Not serious	None	⊕◯◯◯ Very Low
VDR (rs2228570-FokI)	1	Observational	Serious[a]	Very serious[b]	Not serious	Not serious	None	⊕◯◯◯ Very Low
VDR (rs7975232-ApaI)	1	Observational	Serious[a]	Serious[c]	Not serious	Not serious	None	⊕◯◯◯ Very Low
ESR1 (rs9340799, rs2234693); *ESR2* (rs1256049, rs4986938)	1	Observational	Serious[a]	Serious[c]	Not serious	Not serious	None	⊕◯◯◯ Very Low
PTH (rs694, rs6256, rs3072470)	1	Observational	Serious[a]	Serious[c]	Not serious	Serious[d]	None	⊕◯◯◯ Very Low
CYP27B1 (rs4646536); *CYP24A1* (rs927650)	1	Observational	Serious[a]	Serious[c]	Not serious	Serious[d]	None	⊕◯◯◯ Very Low
EGF (rs4444903, rs2237051); *EGFR* (rs2227983)	1	Observational	Serious[a]	Very serious[b]	Not serious	Serious[d]	None	⊕◯◯◯ Very Low
TGFB1 (rs1800469, rs4803455); *TGFBR2* (rs764522, rs3087465)	1	Observational	Serious[a]	Very serious[b]	Not serious	Serious[d]	None	⊕◯◯◯ Very Low

[a]*Serious risk of bias: Lack of clear inclusion/exclusion criteria; inadequate control for confounding variables (nutrition, SES, general health); no reference to validation of dental age assessment method; possible selection bias.*

[b]*Very serious inconsistency: Heterogeneity in age groups studied; conflicting directions of effect; lack of replication across populations.*

[c]*Serious inconsistency: Direction of effects varies across studies or not reported clearly.*

[d]*Serious imprecision: Sample sizes well below the n ≥400 threshold; wide confidence intervals; studies underpowered to detect realistic effect sizes.*

FGFR1/2: Fibroblast Growth Factor Receptor 1/2; IGF2R: Insulin-Like Growth Factor 2 Receptor; FGF3/7/10/13/18: Fibroblast Growth Factor 3, 7, 10, 13, 18; VDR: Vitamin D Receptor; ESR1/2: Estrogen Receptor 1/2; PTH: Parathyroid Hormone; CYP27B1: Cytochrome P450 Family 27 Subfamily B Member 1; CYP24A1: Cytochrome P450 Family 24 Subfamily A Member 1; EGF: Epidermal Growth Factor; EGFR: Epidermal Growth Factor Receptor; TGFB1: Transforming Growth Factor Beta 1; TGFBR2: Transforming Growth Factor Beta Receptor 2.

Methodological considerations also influence interpretation. Candidate gene association studies are particularly vulnerable to false-positive findings due to multiple statistical testing. Because the polymorphisms summarized here were investigated in independent studies with different hypotheses and analytical frameworks, a unified correction across all variants is not methodologically applicable. Nevertheless, several reported associations were based on *p*-values close to conventional thresholds and, without replication, should be considered preliminary and hypothesis-generating. Future primary studies should predefine analytical strategies, apply appropriate corrections for multiple comparisons, and seek replication to enhance reliability.

In this systematic review, thirty-one polymorphisms in nineteen candidate genes were examined, underscoring the broad, yet fragmented, approach to understanding the genetic basis of dental maturation. This broad genetic scope reflects the recognition that dental development is a complex, polygenic trait influenced by multiple pathways, including growth factors, hormonal regulation, and mineral metabolism. The diversity of genes and polymorphisms studied also highlights the challenges in identifying consistent genetic markers due to potential gene–gene interactions and population-specific effects. Importantly, this wide array of investigated variants points to the need for integrative approaches, such as genome-wide association studies (GWAS) and functional analyses, to better capture the genetic architecture underlying dental maturation. To advance the field, it is important to replicate these genetic associations in independent populations, as recommended by the Strengthening the Reporting of Genetic Association Studies (STREGA) guidelines [28]. Replication studies help confirm or refute initial findings, reduce false positives, and increase the reliability of genetic evidence. Therefore, future research with larger samples and rigorous design, following STREGA recommendations, is essential to clarify the genetic contributions to dental age variation.

All included studies were rated as very low certainty of evidence according to GRADE, primarily due to small samples, heterogeneity in design, variability in dental age assessment, and lack of replication. Additionally, differences in ethnic backgrounds and age ranges further complicate the interpretation and generalization of the findings. Cross-sectional designs limited causal inference, and inadequate control for confounding—such as environmental influences, nutrition, and socioeconomic status—further reduced interpretability. These issues represent methodological limitations of the primary literature. Clinical heterogeneity was also present, including one study conducted in children with cleft lip and palate, a congenital craniofacial condition known to influence dental development and eruption patterns. Although this population may not be directly comparable to non-syndromic groups, the study was retained because cleft lip and palate has a strong genetic basis and involves biological pathways fundamental to odontogenesis. Nevertheless, this condition may introduce additional variability and limits generalizability to the broader pediatric population; therefore, its findings should be interpreted with caution.

Dental development is a multifactorial biological process influenced by genetic, systemic, and environmental factors. Across the included studies, several covariates were considered, including sex, chronological age, BMI (Body Mass Index), vitamin D levels, and presence of cleft lip and/or palate. These variables are known to influence somatic growth, bone metabolism, and endocrine regulation, all of which may affect dental maturation. However, the selection and statistical handling of these covariates varied substantially among studies. While some investigations incorporated anthropometric or biochemical parameters, others focused primarily on genetic comparisons with limited adjustment for potential confounders. This heterogeneity reduces comparability between studies and suggests that genetic polymorphisms likely contribute to dental age variation within a broader biological context involving gene–environment and gene–systemic interactions.

In the present systematic review, it was not possible to perform the planned meta-analysis due to the limited number of eligible studies and considerable heterogeneity across them. Although the methodological protocol had anticipated several analytical steps, including sensitivity analyses, meta-regression, and publication bias assessment, these could not be carried out under the available conditions. The small number of studies per outcome prevented meta-regression, as an adequate ratio between the number of covariates and included studies is required [29]. Similarly, funnel plot analysis for publication bias was not feasible, since fewer than ten studies were available per outcome [30]. Furthermore, differences in study design, populations, and outcome assessments contributed to clinical and methodological heterogeneity, limiting the robustness of any pooled estimate. These constraints emphasize the current scarcity of consistent evidence on this topic and highlight the need for future investigations with standardized methodologies and larger, multicenter samples to allow for more reliable meta-analytical approaches.

Given the very low certainty of evidence rated by GRADE, current evidence for associations between genetic polymorphisms and dental age variation is insufficient to draw reliable conclusions. Although seven studies were identified, five of the seven studies (71%) were conducted in Brazil, which significantly limits the generalizability of findings across different ethnic populations. These findings suggest that while certain polymorphisms, such as *FGF18* rs4073716 and *TGFB1* rs4803455 may influence dental development, these associations appear to be context-dependent and possibly modulated by population-specific genetic backgrounds, environmental factors, and ethnic differences. Genetic associations identified in Brazilian populations may not replicate in Central European, Asian, or African populations due to differences in allele frequencies, linkage disequilibrium patterns, and gene-environment interactions. The predominance of studies conducted in Brazilian populations provides valuable regional insights, but may limit the generalizability of findings to broader populations, since ethnic background can also influence dental development and modulate the association between genetic polymorphisms and dental age variation. Additionally, variation in study design, sample sizes, and age ranges, as well as the use of different dental age maturation timing assessment methods, may contribute to heterogeneity in results. The frequent use of the Demirjian method, while widely accepted, may also introduce variability due to its limitations across

ethnic groups. Overall, the current body of literature highlights the complexity of genetic influence on dental maturation and underscores the need for more robust, multicenter studies with standardized methodologies to clarify potential gene–age relationships and their clinical relevance.

Although Demirjian's method remains a global reference for dental age variation estimation, its use as a phenotypic measure in genetic association studies requires methodological validation beyond simple application of the original scoring system. Studies in forensic and digital dentistry have demonstrated that even standardized dental assessment methods demand population-specific validation, evaluation of temporal stability, and quantification of inter- and intra-observer reliability to ensure measurement reproducibility. The absence of such validation may introduce systematic error due to ethnic and developmental variability in dental maturation patterns. In the context of genetic studies, this issue is particularly critical because phenotypic misclassification and measurement imprecision can attenuate true associations, reduce statistical power, and contribute to inconsistent findings across populations.

Because Demirjian's method relies on stage-based classification of tooth development, some degree of observer-related measurement error is unavoidable. In genetic association studies, such non-differential error may attenuate effect estimates and reduce the likelihood of detecting true associations. Although defining mathematical precision thresholds for specific genetic effect sizes lies beyond the scope of this review, the literature indicates that reporting reliability and accuracy metrics is essential to contextualize phenotypic robustness.

An additional limitation of the available literature is the absence of analyses addressing gene–environment interactions, which reflects a gap in the design of the primary studies, rather than the scope of this review. Considering that dental development is influenced by nutritional, hormonal, and socioeconomic factors, the lack of evaluation of these interactions may partly explain the variability and inconsistency of reported genetic associations. Incorporating relevant environmental and developmental variables in future studies may improve the biological interpretation and methodological robustness of genetic findings.

Understanding the genetic influences on dental age variation holds promising potential for future applications. Improved knowledge of how specific polymorphisms affect dental development could lead to more accurate and individualized methods for estimating a child's biological age based on dental maturity. Such advances would have important implications in clinical pediatric dentistry, allowing for tailored treatment planning that aligns with each patient's unique developmental timeline. Moreover, these genetic insights could enhance forensic age estimation techniques, providing more reliable evidence in legal and humanitarian contexts where accurate age determination is critical. Although two specific polymorphisms have shown associations with dental age variation in isolated studies, the low certainty of evidence currently available prevents definitive conclusions about these relationships. Continued research integrating genetic data with clinical and demographic factors, alongside efforts to improve study quality, will be essential to realize the full potential of these findings and translate genetic discoveries into practical tools.

5. Conclusions

Based on the current evidence, it remains unclear whether genetic polymorphisms influence dental age variation. Although two specific polymorphisms were associated with dental age variation in individual studies, the very low certainty of all evaluated outcomes, combined with methodological limitations and lack of replication, prevents definitive conclusions. Further robust and well-designed studies are needed to clarify this potential association.

AVAILABILITY OF DATA AND MATERIALS

Protocol Registration was recorded in the PROSPERO database (https://www.crd.york.ac.uk/prospero/) under the identification number CRD420251041224. The datasets supporting the conclusions of this article are available within the article itself and on **Supplementary material 1**.

AUTHOR CONTRIBUTIONS

LAAA and ECT—designed the research study. LAAA, LMNN, AA, CGCC and ECT—collected and analyzed the data. LAAA—prepared the first draft of the manuscript. LSA, CMA, ECK and FBF—subsequently reviewed and finalized the manuscript. All authors contributed to the revision of previous versions and approved the final manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Livia Azeredo Alves Antunes is serving as one of the Editorial Board mem-

bers of this journal. We declare that Livia Azeredo Alves Antunes had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to AS.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jocpd.com/files/article/2072883408243965952/attachment/Supplementary%20material.zip.

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