Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2025.60.009445

The Role of COL1A1 and COL1A2 Mutations in Craniofacial and Dental Abnormalities in Osteogenesis Imperfecta: A Systematic Review

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ARTICLE INFO

Received: January 21, 2025

Published: January 28, 2025

Citation: Hafsa Shah and Khuder Sadik. The Role of COL1A1 and COL1A2 Mutations in Craniofacial and Dental Abnormalities in Osteogenesis Imperfecta: A Systematic Review. Biomed J Sci & Tech Res 60(3)-2025. BJSTR. MS.ID.009445.

ABSTRACT

Osteogenesis imperfecta (OI), a genetic disorder characterized by brittle bones, often results in craniofacial and dental abnormalities due to mutations in the COL1A1 and COL1A2 genes. This systematic review aimed to evaluate the relationship between these mutations and craniofacial and dental phenotypes in OI patients. Using the PRISMA guidelines, 12 studies meeting inclusion criteria were analyzed and findings revealed that structural mutations, particularly glycine substitutions in COL1A2, were strongly associated with dentinogenesis imperfecta (DI), with a prevalence of 67.6%, compared to 45.4% in COL1A1 mutations. Craniofacial anomalies, including Class II malocclusion and mandibular hypoplasia, were commonly linked to COL1A1 mutations. This review emphasizes the importance of genotype-specific assessments in predicting craniofacial and dental outcomes in OI patients. The findings support the need for personalized dental and orthodontic care and pave the way for targeted genetic and therapeutic research.

Keywords: Osteogenesis Imperfecta; COL1A1; COL1A2

Introduction

Osteogenesis imperfecta (OI), or brittle bone disease, is a rare genetic disorder characterized by fragile bones, low bone density, and craniofacial and dental abnormalities (Marçal, et al. [1]. Its prevalence is approximately 1 in 15,000-20,000 live births (Mahneva, et al. [2]). OI is classified into Sillence types I–IV: Type I is mild, featuring childhood fractures, blue sclera, and occasional dentinogenesis imperfecta (DI). Type II is perinatal lethal, while Type III is the most severe form compatible with survival, involving frequent fractures and severe deformities. Type IV is moderately deforming with variable phenotypes (Mei, et al. [3]). A fifth type, OI Type V, is distinct in lacking DI and presenting unique craniofacial and dental features (Retrouvey, et al. [4]). Approximately 85–90% of OI cases are caused by autosomal dominant mutations in the COL1A1 and COL1A2 genes, which encode the α1(I) and α2(I) chains of type I collagen, a key structural protein critical for skeletal integrity (Mahneva, et al. [2]). Type I collagen constitutes 85% of the skeletal organic matrix, providing tensile strength through its characteristic Gly-X-Y triplet structure (Lindahl, et al. [5]). Glycine's small size is crucial for collagen triple-helix stability; its substitution by larger or charged amino acids disrupts this structure, causing skeletal deformities, blue sclera, and dentinogenesis imperfecta (DI) (Andersson, et al. [2,6]). Figures 1 & 2 show DI frequency and mutation locations (Included after references) [7]. Craniofacial abnormalities, including mandibular hypoplasia, midface deficiency, and malocclusion, significantly affect oral health and quality of life in OI patients (Lindahl, et al. [5]).

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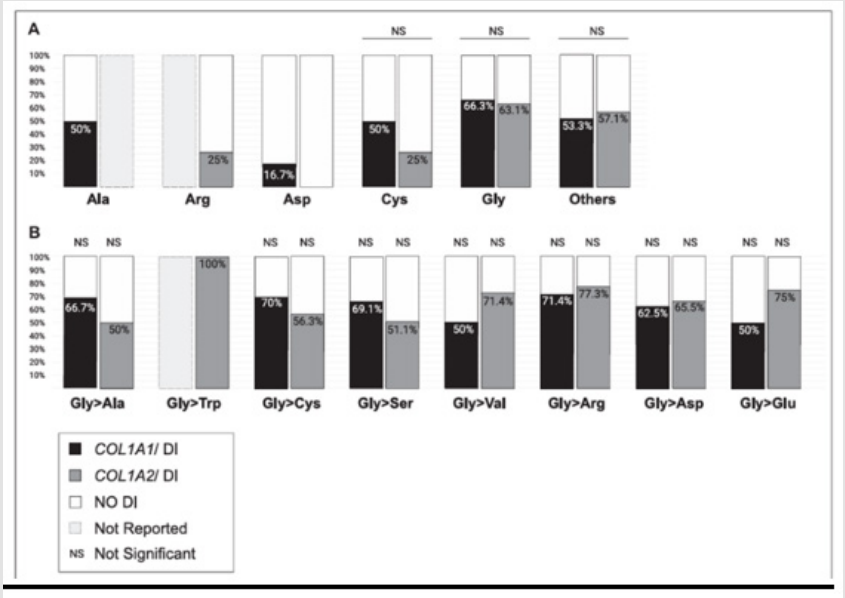

Figure 1: Frequency of DI based on amino acid substitutions in COL1A1 and COL1A2 (Yamaguti, et al. [7]).

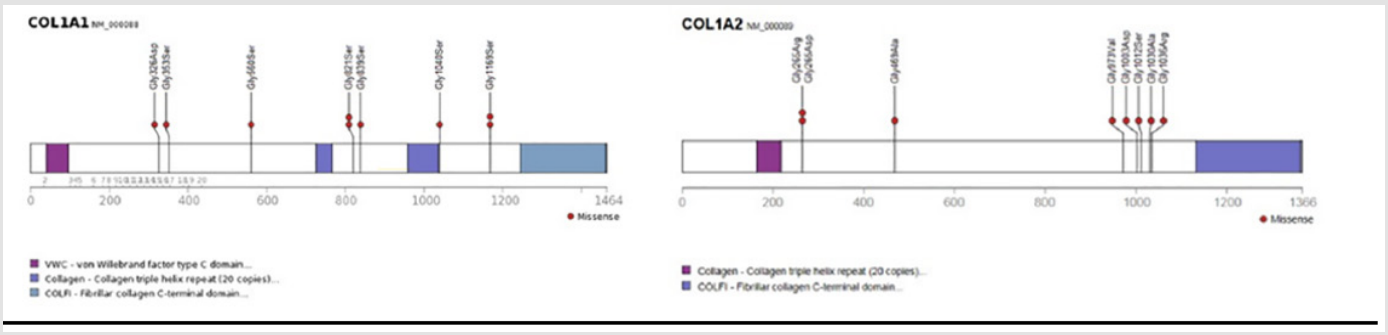

Figure 2: Location of mutations in COL1A1 AND COL1A2 with clear signs of dentinogenesis imperfecta (Andersson, et. al. [4]).

DI, characterized by fragile and discolored teeth, is more prevalent in severe OI types (III and IV) and strongly associated with C-terminal mutations in collagen (Paduano, et al. [5,8]). Phenotypic variability in OI is influenced by the type and location of mutations within COL1A1 and COL1A2. Glycine substitutions account for 74.8% and 89.6% of DI-related mutations in COL1A1 and COL1A2, respectively, highlighting their role in pathological dentinogenesis (Yamaguti, et al. [7]). While these genetic alterations have been studied, detailed analyses linking specific mutations to craniofacial and dental outcomes remain limited. Understanding genotype-phenotype relationships is critical for guiding personalized dental and orthodontic care and developing targeted therapies. This study aims to systematically review the existing evidence on COL1A1 and COL1A2 mutations and their impact on craniofacial and dental phenotypes in OI, identifying knowledge gaps and future research priorities.

Materials and Methods

A systematic review of the literature was conducted using the PubMed Advanced Database. The key terms used in the search included: "Osteogenesis Imperfecta," "genetic mutations," "craniofacial abnormalities," and "dental abnormalities." The search was limited to studies published in English from 2010 to the present. Articles that focused on the relationship between COL1A1 or COL1A2 mutations and craniofacial or dental abnormalities in OI patients were considered for inclusion. The selection process followed the PRISMA guidelines, with a flow diagram created to illustrate the identification, screening, and inclusion of relevant studies. Data extracted from the studies included author information, year of publication, sample size, mutation types, and reported craniofacial and dental abnormalities. Figure 3- Prisma flow diagram (included after references). The find-

ings were synthesized narratively, as the included studies varied in design, population, and reported outcomes. Data was organized by outcome type (e.g., dentinogenesis imperfecta, malocclusion) and by mutation (COL1A1 or COL1A2). Studies were compared qualitatively to identify common findings, trends, and discrepancies in the reported associations between mutations and phenotypic outcomes.

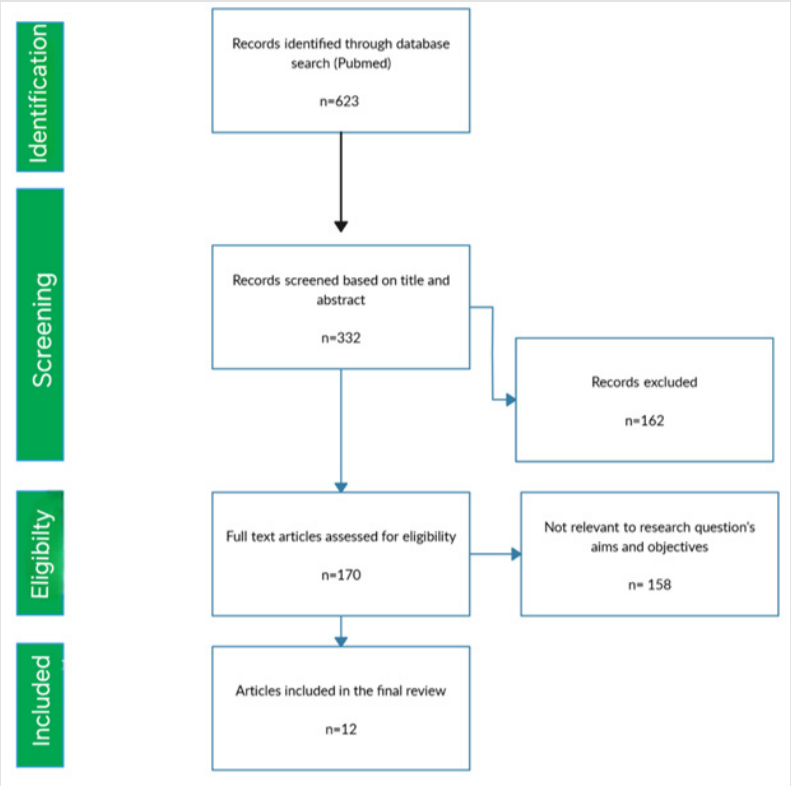

Figure 3: Prisma Flow Chart.

Study Selection and Data Extraction

Studies were Included if they:

1. Reported data on craniofacial and/or dental abnormalities in OI patients.
2. Provided information on COL1A1 or COL1A2 mutations.
3. Were original research articles, including case-control studies, cohort studies, or case reports.

Studies were Excluded if they:

1. Did not report craniofacial or dental outcomes.
2. Did not report information on genetic mutations
3. Focused on non-human subjects.
4. Did not have full-text access available.

Results

Description of Studies Included in the Analysis

A total of 12 studies were included in this review, published between 2010 to present. These studies primarily focused on the relationship between COL1A1 and COL1A2 mutations and craniofacial and dental abnormalities in individuals with osteogenesis imperfecta (OI). Study designs included retrospective cohort studies, case-control studies, observational analyses, and experimental genetic studies, with sample sizes ranging from single case reports to cohorts of 223 participants. The key outcomes assessed across the studies were dentinogenesis imperfecta (DI), malocclusion, hypodontia, and other craniofacial anomalies, such as mandibular hypoplasia and midface deficiency. A common finding was that COL1A2 mutations were more strongly associated with dentinogenesis imperfecta, whereas COL1A1 mutations were linked to a broader range of craniofacial abnormalities (Table 1) [9-12].

Table 1: Description of Studies.

Author	Title	Sample Size	Outcome	P value ; CI (95%)	Mutation Studied	Notes
Andersson, et al. [6]	Mutations in COL1A1 and COL1A2 and dental aberrations in children and adolescents with osteogenesis imperfecta Retrospective cohort study	152	Dental aberrations and craniofacial in OI and dentinogensis imperfecta	0.01	COL1A1 and COL1A2 (p. Gly305)	70% with glycine substitution C-terminal of p.Gly305 had DGI in both dentitions. Collagen I changes noted.
Anderson, et al [9]	Mutations in COL1A1/A2 and CREB3L1 are associated with oligodontia in osteogenesis imperfecta Cross sectional study	10	Hypodontia and oligodontia	n/a	COL1A1, COL1A2, and CREB3L1 (c.3208-6C>T)	Autosomal dominant mutations in COL1A1/2 in 85% of cases. Clinical and genetic findings in individuals further investigated with whole-genome sequencing
Augusciak-Duma, et al. [10]	Mutations in the COL1A1 and COL1A2 genes associated with osteogenesis imperfecta (OI) types I or II Retrospective observational study	8	General OI-related anomalies, reduced collagen secretion	n/a	COL1A1 Mutation E2 Mutation (c.231delG), E22 Mutation (c.1503delT), I51 Mutation (c.4248+1G>A) COL1A2 Mutation E22 Mutation (c.1207G>T, Gly-403Cys):	Mutations were found in exons 2, 22, 50 and in introns 13 and 51 of the COL1A1 gene. In COL1A2, one mutation was identified in exon 22. Gly403Cys mutation linked to severe craniofacial deformities.
Hald, et al. [11]	Skeletal phenotypes in adult patients with osteogenesis imperfecta—correlations with COL1A1/COL1A2 genotype and collagen structure Observational, clinical-genetic correlation study.	85	Skeletal phenotypes, reduced bone mineral density and fractures	$p < 0.001$	COL1A1 (46 mutations), COL1A2 (22 mutations)	OI types I, III, and IV studied; helical mutations associated with severe phenotypes. Qualitative COL-1 defects linked to lower Bone mineral density and bone microarchitecture issues.
Li, et al. [12]	Genotypic Characterization of a Chinese Family with Osteogenesis Imperfecta and Generation of Disease-Specific Induced Pluripotent Stem Cells Experimental, genetic study	3	Phenotypic variability in OI; generation of iPSCs	n/a	COL1A1 (c.725G>T, p.G242V)	A novel COL1A1 mutation (c.725G>T) identified in exon 10. Generated patient-specific iPSC lines to study OI mechanisms and develop therapies.
Lindahl, et al. [5]	Genetic Epidemiology, Prevalence, and Genotype–Phenotype Correlations in the Swedish Population with Osteogenesis Imperfecta Cohort study	223 individuals	- 25% had Dentinogenesis Imperfecta (DI)	$P < 0.0001$	COL1A1 and COL1A2 mutations	- DI strongly associated with qualitative mutations & more common in severe OI (types III and IV) - C-terminal helical mutations were associated with DI in both genes -DI was found to be more common in females with mild type I OI (58%).

Mahneva, et al. [2]	Discrepancies in the Phenotypical Classification of Osteogenesis Imperfecta in a Patient with COL1A2 Mutation Case Report	1 (case study)	Dentinogenesis imperfecta (DI)	N/A	COL1A2 mutation (c.982G>A, p.G328S)	- Unique combination of severe perinatal and mild postnatal phenotypes - Difficulty in classifying OI type using standard criteria
Marçal, et al. [1]	Dental Alterations on Panoramic Radiographs of Patients with Osteogenesis Imperfecta in Relation to Clinical Diagnosis, Severity, and Bisphosphonate Regimen Aspects Case control study	24 OI patients, 48 controls	- High prevalence of dental abnormalities: dentinogenesis imperfecta (75%), tooth impaction, ectopic teeth - Bisphosphonate therapy linked to specific alterations	- DI: P < 0.001; OR = 1.62 (0.16–16.28) Pulp obliteration: P = 0.001; OR = 58.75 (5.45–633.11)	COL1A1, COL1A2	- Bisphosphonate use associated with delayed tooth eruption and developmental changes - Emphasized systematic dental exams in OI patients
Mei, et al. [3]	Comparing Clinical and Genetic Characteristics of De Novo and Inherited COL1A1/COL1A2 Variants in a Large Chinese Cohort of Osteogenesis Imperfecta Retrospective Cohort	135	Clinical severity higher in de novo mutations; more frequent Type III OI higher clinical scores	p<0.001 for Type III OI	COL1A1 and COL1A2	De novo mutations have higher phenotypic severity due to lack of purifying selection; structural mutations (e.g., glycine substitutions) dominate; missense mutations prevalent in both groups
Paduano, et al. [8]	Expanding the genetic and clinical spectrum of osteogenesis imperfecta: identification of novel rare pathogenic variants in type I collagen-encoding genes Retrospective cohort study	10	Novel rare pathogenic variants identified in COL1A1 (5 PVs) and COL1A2 (2 PVs), expanding known mutation spectrum	n/a	COL1A1 (c.2890_2893del, c.3887del), COL1A2 (c.596G>T)	R New frameshift and missense variants reported; these mutations contribute to protein truncation or altered function, affecting the type I collagen framework. Genetic findings highlight novel therapeutic targets and diagnostic implications.
Retrouvey, et al. [4]	Oro-dental and cranio-facial characteristics of osteogenesis imperfecta type V Observational cohort study	14	Missing permanent teeth, Class II malocclusion, retrusive profile; no dentinogenesis imperfecta	N/A	IFITM5 (c.-14C > T)	67% had missing teeth; 57% showed Class II malocclusion and retrusive facial profile; decreased lower face height in 57%. Distinct phenotype from COL1A1/2 mutations; premolar agenesis prominent
Yamaguti, et al. [7]	Unequal Impact of COL1A1 and COL1A2 Variants on Dentinogenesis Imperfecta Retrospective cohort study with an added meta-analysis	81 patients (cohort), 906 (meta-analysis)	DI prevalence: 45.4% (COL1A1) and 67.6% (COL1A2); hotspots identified; DI linked to qualitative mutations	p<0.0001	COL1A1, COL1A2	DI is more common in COL1A2 variants, especially severe OI types (III, IV); identified 4 DI hotspots (e.g., p.Gly767Ser, p.Gly821Ser in COL1A1); novel correlation with major ligand binding regions influencing DI risk.

Findings Across Studies

The studies consistently reported that COL1A2 mutations were more frequently linked to dentinogenesis imperfecta (DI) than COL1A1 mutations (Andersson, et al. [1,6,7]) found that DI was present in 67.6% of individuals with COL1A2 mutations, compared to 45.4% in those with COL1A1 mutations. with qualitative mutations, particularly missense variants, being strongly associated with DI occurrence ($p < 0.0001$). COL1A1 mutations, particularly those involving glycine substitutions near p.Gly305, were strongly associated with DI in both primary and permanent dentitions (Andersson, et al. [6]).Craniofacial abnormalities, such as malocclusion and mandibular hypoplasia, were also more commonly associated with COL1A1 mutations (Augusciak-Duma, et al. [5, 10]). Hypodontia and tooth impaction were linked to both COL1A1 and COL1A2 mutations (Marçal, et al. [1]). Overall, the studies reviewed show consistent evidence linking COL1A1 and COL1A2 mutations to significant craniofacial and dental abnormalities in OI patients. COL1A2 mutations were more strongly associated with dentinogenesis imperfecta, while COL1A1 mutations were linked to a broader range of craniofacial abnormalities. Some studies also investigated novel mutations and their implications for the OI phenotype (Li, et al. [8,12]). These findings emphasize the importance of genetic testing in diagnosis, phenotypic classification, and personalized management of OI-related anomalies.

Discussion

This systematic review highlights the significant association between COL1A1 and COL1A2 mutations and the development of craniofacial and dental abnormalities in osteogenesis imperfecta (OI). Over 85% of OI cases are linked to mutations in these genes, which encode procollagen type I. Mutations affecting the triple helix domain, particularly missense mutations, impair collagen incorporation into procollagen, contributing to severe phenotypes like OI Type III (Augusciak-Duma, et al. [10]).Both COL1A1 and COL1A2 mutations lead to structural or quantitative defects in type I collagen, a critical component in tooth development. During the late bell stage, type I collagen plays an essential role in facilitating predentin secretion (Andersson, et al. [9]). These mutations are significant contributors to dentinogenesis imperfecta (DI), observed in approximately 75% of moderate-to-severe OI cases (Marçal, et al. [1,8]). Notably, COL1A2 glycine substitutions are strongly linked to DI, characterized by brittle and discolored teeth (Yamaguti, et al. [7]). In contrast, COL1A1 mutations are implicated in a broader spectrum of craniofacial abnormalities, including malocclusion, mandibular hypoplasia, and midface deficiency (Lindahl, et al. [5,10]). Notably, glycine substitutions near p.Gly305 in COL1A1 result in DI in both dentitions, affecting 70% of individuals. These mutations are also associated with permanent molar retention and taurodontism, underscoring the role of type I collagen in tooth morphogenesis (Andersson, et al. [9]). Shared features, such as hypodontia and tooth impaction, further illustrate the complex genotype-phenotype relationships in OI (Marçal, et al. [1]).

The findings emphasize the importance of genetic testing in predicting and managing craniofacial and dental abnormalities. For instance, COL1A2 mutations necessitate vigilant monitoring for DI, while craniofacial anomalies benefit from a multidisciplinary approach involving geneticists, dentists, and orthopedic specialists. Additionally, bisphosphonate therapy requires careful monitoring to mitigate potential delays in tooth eruption and developmental anomalies (Marçal, et al. [1]). Emerging research on patient-specific induced pluripotent stem cells (iPSCs) offers promise for understanding the mechanisms of OI and developing targeted therapies. Li, et al. [12] demonstrated the utility of iPSCs in preserving donor-specific genetic traits, enabling the exploration of biochemical pathways and the development of targeted treatments. Novel mutations, such as COL1A1 (p.G242V), continue to expand the genetic spectrum of DI and OI, identifying new therapeutic targets (Li, et al. [8,12]). Despite these advances, several limitations persist. Small sample sizes and inconsistent diagnostic criteria for craniofacial and dental abnormalities hinder the generalizability of findings and complicate cross-study comparisons. Retrospective studies often introduce biases and incomplete phenotype documentation, further limiting conclusions. Future research should prioritize larger, multicenter studies to address these gaps. Standardizing diagnostic criteria and elucidating molecular mechanisms underlying OI's phenotypic diversity are critical for refining diagnostic and therapeutic strategies.

Conclusion

This systematic review was done to understand the significant association between COL1A1 and COL1A2 mutations and craniofacial and dental abnormalities in osteogenesis imperfecta (OI). COL1A2 mutations, particularly glycine substitutions, were strongly linked to dentinogenesis imperfecta, while COL1A1 mutations were associated with a broader spectrum of craniofacial defects such as malocclusion and mandibular hypoplasia. These findings highlight the importance of genetic testing for guiding personalized treatment plans, including early dental interventions and orthodontic care. Future research should focus on large-scale, longitudinal studies to further explore genotype-phenotype correlations and improve the clinical management of OI-related abnormalities.

Conflict of Interest

The authors declared no conflict of interest.

Funding

None.

Author Contributions

All authors drafted the manuscript, critically revised the manuscript and reviewed the literature. All authors read and approved the final manuscript.

1. All authors have participated in the work and have reviewed and agree with the content of the article.

2. None of the article contents are under consideration for publication in any other journal or have been published in any journal.

3. No portion of the text has been copied from other material in the literature (unless in quotation marks, with citation).

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Data Availability Statement

The authors declare that all the data supporting the findings of this study are available within the manuscript.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2025.60.009445

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