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TRANSFORMING GROWTH FACTOR BETA RECEPTOR II (TGFBR2) AND KIRSTEN RAT SARCOMA VIRUS (KRAS) IN CEMENTO-OSSEOUS DYSPLASIA OF THE JAW – A SYSTEMATIC REVIEW

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ABSTRACT

Background: Cemento-osseous dysplasia (COD) is the most common benign fibro-osseous lesion of the jaw, predominantly affecting women in the fourth to sixth decades of life. Despite being a well-recognized entity radiologically and histologically, the genetic mechanisms underpinning COD are poorly understood. Recent advances in genomic sequencing have identified somatic mutations in components of the RAS-MAPK signaling pathway and the TGF-β receptor family, notably KRAS and TGFBR2. These discoveries raise important questions regarding the biological basis of COD and its distinction from other fibro-osseous lesions such as cemento-ossifying fibroma.

Objective: This systematic review aimed to evaluate and synthesize current evidence on the involvement of TGFBR2 and KRAS in COD, with emphasis on molecular pathogenesis, diagnostic implications, and potential clinical relevance.

Methods: A systematic literature search was performed in PubMed, Scopus, Embase, and Google Scholar up to August 2025. The study followed PRISMA 2020 guidelines, and the protocol was registered in PROSPERO **(**CRD420251140937**)**. Eligible studies included original research, case series, or case reports describing TGFBR2 and/or KRAS alterations in COD. Data extraction focused on study design, genetic variants identified, allelic frequency, and conclusions drawn by the authors.

Results: Out of 127 records screened, five studies met the inclusion criteria. Owosho et al. (2025) reported TGFBR2 hotspot variants (p.Arg528His, p.Arg553His) and noncanonical KRAS mutations (splice variant and p.Lys167Arg) in COD, although at low allelic frequencies. Haefliger et al. (2023) provided broader evidence that RAS-MAPK pathway activation is a recurrent mechanism in COD, implicating KRAS alongside BRAF, HRAS, and FGFR3. Breimer et al. (2025) identified a novel NOTCH4 splice mutation, highlighting molecular heterogeneity. Large clinicopathological analyses by Gomes (2024) and Decolibus (2023) emphasized diagnostic overlap between COD and cemento-ossifying fibroma and advocated for molecular profiling to refine classification.

Conclusions: Current evidence suggests that TGFBR2 and KRAS alterations contribute to COD pathogenesis, likely through dysregulation of RAS-MAPK and TGF-β signaling. These mutations, however, are subclonal and infrequent, implying that additional genetic drivers remain unidentified. Incorporating molecular profiling into diagnostic practice could aid in differentiating COD from other fibro-osseous lesions. Larger, multi-institutional sequencing studies are warranted to validate these findings and explore therapeutic relevance.

Keywords: Cemento-osseous dysplasia, TGFBR2, KRAS, fibro-osseous lesions, RAS-MAPK pathway, molecular pathogenesis

INTRODUCTION

Fibro-osseous lesions of the jaws encompass a diverse group of conditions in which normal bone is progressively replaced by fibrous connective tissue and mineralized products[1]. Among these, cemento-osseous dysplasia (COD) represents the most prevalent lesion, typically arising in tooth-bearing regions of the mandible and maxilla. COD is a benign, non-neoplastic entity and is often identified incidentally during radiographic examinations, as most patients remain asymptomatic. In certain cases, however, complications such as secondary infection, cortical expansion, or pain may occur, particularly in florid or multifocal variants[2].

COD demonstrates a distinct demographic predilection, occurring most frequently in women during the fourth and fifth decades of life, with a higher incidence among individuals of African and Asian descent. Based on distribution, COD is classified into periapical, focal, florid, and familial florid subtypes[3]. Radiographically, these lesions progress through a characteristic sequence: an initial radiolucent stage, a mixed radiolucent-radiopaque stage, and ultimately, a mature sclerotic phase. Histologically, COD exhibits a fibrous stroma with irregular trabeculae of woven bone and cementum-like material, often without prominent osteoblastic rimming[4].

Although the clinical and pathological features of COD are well described, its etiopathogenesis remains poorly defined. For decades, COD was thought to represent a reactive or dysplastic process of periodontal ligament origin, with local irritants, vascular changes, or occlusal trauma considered as potential triggers[5]. This interpretation aligned with its non-progressive behavior and tendency to stabilize without intervention. However, advances in molecular biology have begun to challenge this paradigm.

Emerging evidence indicates that COD may not be purely reactive but could instead represent a clonally driven process in at least a subset of cases. The discovery of somatic mutations in genes regulating osteogenic differentiation, bone remodeling, and intracellular signaling cascades suggests a genetic component to COD development. In particular, genes within the RAS-MAPK signaling pathway and the transforming growth factor-beta (TGF-β) receptor family have attracted attention due to their central roles in skeletal biology[3].

The RAS-MAPK pathway is a fundamental regulator of cell proliferation, differentiation, and survival. Mutations in RAS family genes, particularly KRAS, result in constitutive activation of downstream signaling, which has been implicated in the pathogenesis of a variety of craniofacial bone lesions and neoplasms[6]. Similarly, TGFBR2, encoding a receptor for the TGF-β superfamily, is essential for maintaining the balance between bone resorption and formation. Alterations in this receptor can disrupt osteoblast-osteoclast communication and extracellular matrix production, potentially predisposing to dysplastic mineralization[7].

Understanding whether such mutations contribute directly to COD is of clinical importance. First, it may clarify the biological nature of COD whether it is entirely reactive or partially neoplastic. Second, molecular characterization could assist in distinguishing COD from cemento-ossifying fibroma (COF), a benign but true neoplasm that often mimics COD radiographically and histologically. Finally, exploring the molecular landscape of COD may reveal potential targets for future diagnostics or even therapeutic interventions.

Given the rising interest in the genetic underpinnings of fibro-osseous lesions, a systematic synthesis of current knowledge regarding TGFBR2 and KRAS in COD is warranted. This review aims to consolidate available evidence, evaluate the contribution of these genes to COD pathogenesis, and place their significance within the broader context of fibro-osseous jaw lesions.

MATERIALS AND METHODS

This systematic review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[8]. A PRISMA flow diagram (Figure 1) illustrates the study selection process. The review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO, Registration ID: CRD420251140937).

Research Question and PICOS Framework

The research question was structured using the PICOS framework[9]:

- **Population (P):** Patients diagnosed with cemento-osseous dysplasia of the jaws (any subtype: periapical, focal, florid, familial florid).
- **Intervention/Exposure (I):** Genetic or molecular investigations focusing on TGFBR2 and KRAS alterations (including targeted sequencing, panel-based next-generation sequencing, or whole-exome sequencing).
- **Comparison (C):** Not applicable (as most studies were descriptive without control groups); when available, comparisons to other fibro-osseous lesions (e.g., cemento-ossifying fibroma, fibrous dysplasia) were considered.
- **Outcomes (O):** Identification of pathogenic or likely pathogenic variants in TGFBR2 and KRAS; allelic frequency; functional or clinical relevance to COD pathogenesis.
- **Study design (S):** Case reports, case series, retrospective cohorts, or molecular pathology studies providing original genetic data.

Search Strategy and Information Sources

A comprehensive literature search was conducted in the following databases: PubMed/MEDLINE, Scopus, Embase, and Google Scholar from inception until August 2025. Search terms combined free-text keywords and controlled vocabulary (MeSH terms where available). The Boolean operators “AND” and “OR” were applied. The main search strategy included:

- *“cemento-osseous dysplasia” OR “fibro-osseous lesion”*
- AND *“TGFBR2” OR “transforming growth factor beta receptor 2”*
- AND *“KRAS” OR “RAS-MAPK pathway”*

The reference lists of all eligible articles were also screened to identify additional studies.

Eligibility Criteria

Inclusion criteria:

- Studies involving human participants with histopathologically confirmed COD.
- Articles reporting molecular or genetic analysis of COD, specifically addressing TGFBR2 and/or KRAS.
- Original research, case reports, case series, or retrospective cohorts published in English.

Exclusion criteria:

- Reviews, editorials, or conference abstracts lacking primary data.
- Studies involving fibro-osseous lesions other than COD without clear COD-specific results.
- Articles without genetic or molecular analysis.

Study Selection

Two reviewers independently screened titles and abstracts to identify potentially relevant articles. Full-text review was conducted for all shortlisted studies. Discrepancies were resolved through discussion and consensus.

Data Extraction and Synthesis

Data from eligible studies were extracted into a structured table, including:

- Author and year of publication
- Study design and sample size
- Patient demographics (where available)
- Method of genetic testing (e.g., targeted sequencing, NGS panel, whole-exome sequencing)
- Reported TGFBR2 and KRAS variants, with allelic frequency
- Conclusions drawn regarding pathogenesis and clinical significance

Due to the rarity of COD and the limited number of available genetic studies, a qualitative synthesis was performed. Quantitative meta-analysis was not feasible given heterogeneity in methodology, study design, and outcome reporting.

Risk of Bias and Quality Assessment

As most included studies were case reports or small case series, the risk of bias was assessed qualitatively. Evaluation criteria included clarity of COD diagnosis, robustness of genetic methodology, variant classification standards (e.g., ACMG guidelines), and transparency of reporting. Potential publication bias was acknowledged, as cases with positive molecular findings are more likely to be published.

RESULTS

Study selection

From 127 records, 5 studies were included after screening and eligibility assessment (Figure 1).

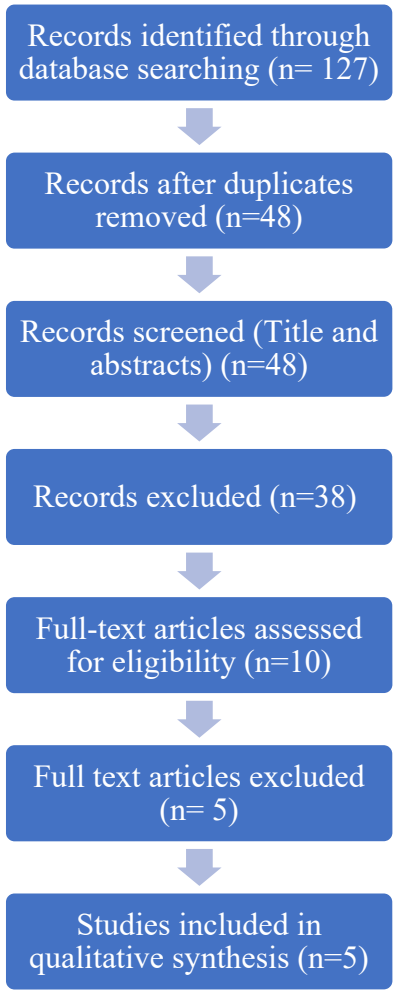

Figure 1: PRISMA Flowchart

Study characteristics
Table 1 summarizes included studies.

- Owosho et al. (2025) performed targeted sequencing on COD samples and identified TGFBR2 mutations (p.Arg528His, p.Arg553His) and KRAS variants (splice and p.Lys167Arg), though at low allelic frequencies (1.4–10%).
- Haefliger et al. (2023) analyzed 18 COD cases and identified RAS-MAPK pathway activation in 28%, including KRAS, HRAS, BRAF, and FGFR3 mutations.
- Breimer et al. (2025) described a COD case with a novel NOTCH4 splice mutation, broadening the genetic spectrum.
- Decolibus (2023) conducted whole-exome sequencing in florid COD, revealing copy number alterations but no recurrent TGFBR2 or KRAS mutations.
- Gomes (2024) presented a clinicopathological analysis of 191 COD cases, emphasizing the diagnostic challenge of distinguishing COD from cemento-ossifying fibroma, though without molecular profiling.

Table 1. Characteristics of Included Studies on COD and Genetic Alterations

Author (Year)	Study	Study Design	Sample Size / Demographics	Aim of Study	Methodology	Main Findings	Clinical Significance
Owosho (2025)[10]	Alterations of TGFBR2 and KRAS in cemento-osseous dysplasia of the jaw.	Case series with targeted sequencing	2 patients with histologically confirmed COD	To investigate genetic alterations in COD using a broad sequencing panel	DNA isolated from FFPE COD tissue; tumor-only variant calling pipeline for 1,036 genes	Detected TGFBR2 p.Arg528His, p.Arg553His (3% AF) and KRAS splice variant (10% AF), p.Lys167Arg (1.4% AF)	Provided first evidence of TGFBR2 involvement in COD; suggested KRAS/TGFBR2 may contribute to later-stage progression
Breimer (2025)[11]	Cemento-osseous dysplasia with a NOTCH4	Case report	32-year-old female with COD	To describe incidental COD lesion	TruSight Oncology 500 panel; NovaSeq X	Novel NOTCH4 splice-site mutation	Expanded COD molecular spectrum;

	mutation: a case report			with molecular profiling	platform	(c.2021+1G>A) identified	highlighted potential role of Notch signaling in fibro-osseous lesions
Gomes (2024)[12]	Whole-exome sequencing and copy number alterations analysis in a case of expansive florid cemento-osseous dysplasia	Large retrospective clinicopathological series	191 COD cases	To describe demographic and clinical characteristics of COD	Clinicopathological review; no genetic sequencing	COD most common in middle-aged women; highlighted diagnostic overlap with cemento-ossifying fibroma	Reinforced importance of accurate diagnosis; underscored need for molecular profiling to distinguish COD from COF
Haefliger (2023)[13]	Cemento-osseous dysplasia is caused by RAS-MAPK activation.	Retrospective cohort	18 COD cases	To identify recurrent mutations in COD using targeted sequencing	NGS panel covering RAS-MAPK pathway genes	28% of COD cases showed mutations in KRAS, HRAS, BRAF, FGFR3	Confirmed RAS-MAPK activation as a common mechanism in COD pathogenesis
Decolibus (2023)[14]	Cemento-Osseous Dysplasia of the Jaw: Demographic and Clinical Analysis of 191 New Cases.	Whole-exome sequencing case study	1 case of florid COD	To explore copy number changes and mutations in florid COD	WES + CNV analysis	No recurrent TGFBR2/KRAS variants; identified chromosomal copy number alterations	Suggested genomic instability may contribute to florid COD, though specific gene drivers remain unclear

Table 2. Summary of Genetic Alterations in COD

Gene	Variant(s) Reported	Frequency / Allelic Burden	Functional Pathway	Biological/Clinical Relevance
TGFBR2[10]	p.Arg528His, p.Arg553His	Rare, ~3% AF in COD samples	TGF-β signaling (regulates bone remodeling, osteoblast activity)	Suggests dysregulation of TGF-β pathway may contribute to COD progression or heterogeneity
KRAS[10,13]	Splice mutation; p.Lys167Arg	AF 1.4–10% in COD	RAS-MAPK cascade (cell proliferation, differentiation)	Supports role of MAPK pathway activation in COD; parallels with other fibro-osseous lesions like fibrous dysplasia
NOTCH4[11]	c.2021+1G>A splice-site mutation	Identified in single COD case	Notch signaling (stem cell fate, osteogenesis inhibition)	Expands molecular landscape of COD; indicates potential overlap with ossifying fibroma
HRAS[13]	Missense variants (not specified)	Part of 28% mutation rate in cohort	RAS-MAPK signalling	Additional evidence for MAPK pathway involvement
BRAF[13]	V600E-like variants (reported in cohort)	Rare, subset of COD	RAS-MAPK signaling	Well-known oncogenic driver; may play role in COD subset
FGFR3[13]	Missense variants	Found in COD cohort	Growth factor signaling linked to MAPK	Suggests FGFR3-MAPK axis may influence COD development

DISCUSSION

This systematic review consolidates the current understanding of TGFBR2 and KRAS alterations in cemento-osseous dysplasia (COD) and situates them within the broader molecular framework of fibro-osseous lesions of the jaws. Although COD has long been classified as a non-

neoplastic, self-limiting condition, emerging genetic evidence suggests that it may not be entirely reactive in origin. Instead, subsets of COD may represent clonally influenced lesions, driven in part by dysregulation of the RAS-MAPK and TGF-β signaling pathways.

One of the consistent findings across studies is the involvement of the RAS-MAPK pathway. Haefliger et al.[13] demonstrated that nearly one-third of COD cases harbor mutations in RAS-MAPK–related genes, including KRAS, HRAS, BRAF, and FGFR3, establishing pathway activation as a recurring event in COD. Owosho et al.[10] reported noncanonical KRAS variants, including a splice-site mutation and p.Lys167Arg, albeit at low allelic frequencies. The convergence of these studies suggests that KRAS alterations, while not universal, may play a subclonal role in lesion progression. Importantly, the low variant allele fractions reported imply that only a minority of lesional cells carry these alterations, supporting the view that RAS-MAPK activation contributes to heterogeneity and progression rather than initiation.

In addition to KRAS, Owosho et al.[10] identified hotspot mutations in TGFBR2 (p.Arg528His and p.Arg553His). These variants, typically associated with malignancies, were unexpected in COD, a benign lesion. Their detection at low frequencies suggests they may be late or modifying events, influencing lesion biology rather than driving initiation. Nevertheless, given the crucial role of TGFBR2 in regulating osteoblast differentiation and extracellular matrix production, its alteration could synergize with MAPK activation, amplifying abnormal bone and cementum deposition. This raises the intriguing possibility that cross-talk between TGF-β and MAPK pathways underpins the dysplastic but non-aggressive nature of COD.

While TGFBR2 and KRAS mutations have attracted attention, COD is not genetically homogeneous. Breimer et al.[11] described a NOTCH4 splice mutation in COD, implicating Notch signaling in its pathogenesis. Since Notch pathways regulate stem cell differentiation and osteogenesis, their involvement broadens the molecular spectrum of COD beyond TGF-β and MAPK signaling. Decolibus et al.[14], using whole-exome sequencing in florid COD, identified copy number variations but no recurrent point mutations in TGFBR2 or KRAS, further illustrating genetic variability. Collectively, these findings emphasize that COD should not be considered a uniform entity but rather a molecularly diverse group of lesions with overlapping histological features.

The clinical importance of these findings lies in the distinction between COD and cemento-ossifying fibroma (COF). While COD is asymptomatic, self-limiting, and requires only observation, COF is a true benign neoplasm with progressive growth that mandates surgical removal. Both lesions, however, share similar clinical, radiographic, and histological features, often leading to diagnostic uncertainty. Gomes et al.'s[12] large clinicopathological series highlighted this diagnostic overlap and the challenges it poses in clinical practice. The integration of molecular profiling offers a valuable adjunct in resolving such ambiguity. The detection of KRAS, TGFBR2, or NOTCH4 mutations in a lesion supports a COD diagnosis, whereas their absence combined with expansile behavior may favor COF.

To illustrate these differences, Table 3 compares COD and COF across clinical, histological, and molecular parameters.

Table 3. Comparative Features of Cemento-Osseous Dysplasia (COD) and Cemento-Ossifying Fibroma (COF)

Feature	Cemento-Osseous Dysplasia (COD)[14,16]	Cemento-Ossifying Fibroma (COF)[15]
Nature	Benign, non-neoplastic, dysplastic process of periodontal ligament origin	True benign neoplasm (fibro-osseous tumor)
Demographics	Middle-aged women, higher prevalence in African and Asian populations	Younger adults, slight female predilection, broader ethnic distribution
Location	Tooth-bearing regions of mandible > maxilla; often periapical, focal, or florid	Mandible (posterior region) common; may involve maxilla
Clinical presentation	Usually asymptomatic; incidental finding; may present with swelling, infection in florid subtype	Often presents with painless swelling, facial asymmetry, or expansion; may displace teeth
Radiographic features	Radiolucent → mixed → radiopaque with diffuse, poorly defined margins	Well-circumscribed, expansile lesion with corticated borders; concentric growth pattern
Histopathology	Fibrocellular stroma with irregular woven bone and cementum-like deposits; minimal osteoblastic rimming	Fibro-osseous tissue with trabeculae of bone or cementum-like material; usually with osteoblastic rimming; encapsulated
Behavior	Self-limiting, stabilizes spontaneously; rarely requires intervention unless secondarily infected	Progressive, expansile growth; requires surgical excision due to potential recurrence
Molecular profile	Reported mutations in TGFBR2, KRAS, HRAS, BRAF, FGFR3, and occasionally NOTCH4; generally low allelic frequency	No consistent recurrent mutations identified; some reports suggest chromosomal copy number changes; absence of COD-specific molecular profile
Management	Conservative; radiographic monitoring; avoid unnecessary biopsy	Surgical excision or enucleation; recurrence possible if incomplete removal
Prognosis	Excellent; conservative follow-up sufficient	Excellent with complete excision, though recurrence can occur

When the findings of included studies are considered together, a consistent picture emerges: COD lesions frequently harbor mutations within the RAS-MAPK axis, albeit at variable and often low allele frequencies. This was confirmed by Haefliger et al.'s[13] cohort study and Owosho et al.'s[10] case-based sequencing. Importantly, the studies complement each other Haefliger et al.[13] demonstrated the overall prevalence of RAS-MAPK pathway involvement in COD, while Owosho et al.[10] provided the first evidence of concurrent TGFBR2 alterations. In contrast, Decolibus et al.'s[14] whole-exome analysis, which did not reveal recurrent mutations in these genes, suggests that not all COD lesions are genetically altered in detectable pathways, raising the possibility of yet unidentified drivers. Breimer et al.'s[11] description of NOTCH4 involvement highlights this diversity. Together, these studies confirm that COD is not a monolithic lesion but a condition with multiple molecular routes leading to a shared histopathological outcome.

Future perspectives

The findings of this review underscore the need for larger, multi-institutional sequencing studies to determine the true prevalence and significance of TGFBR2 and KRAS mutations in COD. Future research should extend beyond single-gene or panel sequencing to incorporate whole-genome, transcriptomic, epigenomic, and methylation profiling. Such multi-omic approaches may clarify whether COD consists of molecularly distinct subtypes that correlate with its clinical variants (periapical, focal, florid, familial).
In addition, functional studies using in vitro cell models or in vivo animal systems are required to determine whether TGFBR2 and KRAS mutations alter osteogenic differentiation, extracellular matrix production, or stromal-epithelial interactions. From a clinical standpoint, development of molecular diagnostic markers could greatly improve differentiation between COD and COF in challenging cases. In the long term, understanding the molecular basis of COD may pave the way for personalized diagnostic algorithms, ensuring patients receive appropriate, minimally invasive care while avoiding overtreatment.

CONCLUSION

Available evidence indicates that TGFBR2 and KRAS mutations occur in cemento-osseous dysplasia, generally at low variant-allele fractions, implicating dysregulation of the RAS-MAPK and TGF-β pathways and underscoring the lesion's genetic heterogeneity. Although not ubiquitous, these alterations have potential diagnostic utility particularly for refining classification and distinguishing COD from morphologically similar fibro-osseous entities. To establish pathogenic relevance and clinical applicability, prospective, multicenter investigations employing standardized tissue handling, sensitive next-generation sequencing**,** multi-omic profiling, and functional validation are warranted.

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