

Jones Syndrome: a systematic literature review

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Abstract

Background: Jones syndrome is an extremely rare genetic condition characterized by the coexistence of gingival fibromatosis and progressive sensorineural hearing loss. It is an autosomal dominant disorder whose genetic basis has been identified, through exome sequencing technology, as pathogenic mutations in exon 5 of the Repressor Element 1 Silencing Transcription Factor (REST) gene. This review aimed to evaluate whether integrating genetic testing improves the diagnostic accuracy of Jones syndrome compared with clinical assessment alone. **Methods:** An electronic and manual search was conducted in August 2025 across multiple databases (PubMed, Cochrane Library, Google Scholar, Scopus, and Web of Science) in accordance with PRISMA guidelines. Two independent reviewers performed the search. From eligible studies, the following data were extracted: author and year of publication, study design, patient age and sex, oral manifestations, systemic manifestations, diagnostic and therapeutic approaches, severity of gingival fibromatosis, and degree of sensorineural hearing loss (SNHL). Any disagreements were resolved through discussion with a third reviewer and by consensus. **Results:** The electronic and manual search retrieved 9,864 records. After removal of duplicates (n = 15) and title screening, 9,837 articles were excluded, leaving 12 articles for abstract and full-text screening. Two articles were excluded because their full texts were unavailable. After full-text assessment, four additional articles were excluded, resulting in six studies included in the review. The included studies comprised four case reports without genetic analysis and two studies that included analysis of the Repressor Element 1 Silencing Transcription Factor (REST) gene, documenting familial cosegregation. **Conclusions:** REST gene analysis currently represents an essential diagnostic tool, as it complements the clinical workup, increases diagnostic accuracy, and opens new perspectives for the management and support of patients with Jones syndrome.

Keywords: Jones Syndrome; systematic review; gingival fibromatosis.

Introduction

Jones syndrome is an extremely rare genetic condition characterized by the coexistence of gingival fibromatosis and progressive sensorineural hearing loss (1). It is an autosomal dominant disorder whose genetic basis has been identified, through exome sequencing technology, as pathogenic mutations in exon 5 of the Repressor



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Element 1 Silencing Transcription Factor (REST) gene, a transcriptional repressor (2-4).

The literature still provides limited clinical and genetic information on this condition. Within this context, the present review aims to synthesize the available evidence and provide an updated overview of Jones syndrome, thereby contributing to improvements in diagnosis, treatment, and the understanding of the pathogenetic mechanisms of this rare yet clinically significant disorder.

Materials and methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (5).

Population, Intervention, Comparison, Outcomes (PICO)

The research question guiding this review was defined as follows:

“In patients with gingival fibromatosis and sensorineural hearing loss, does diagnosis based on REST gene analysis offer greater accuracy and clinical utility compared with clinical evaluation alone?”

The research question was formulated according to the PICO (Population, Intervention, Comparison, Outcomes) framework:

- P (Population): Patients with gingival fibromatosis associated with sensorineural hearing loss (suspected Jones syndrome).
- I (Intervention): Diagnosis through REST gene analysis.
- C (Comparison): Diagnosis based exclusively on clinical evaluation (oral manifestations and hearing impairment without genetic testing).
- O (Outcomes): Severity of gingival fibromatosis and sensorineural hearing loss; etiologic confirmation.

Inclusion Criteria

Before initiating the review, inclusion and exclusion criteria were established.

To be included, studies had to be published in English or Italian, involve young and/or adult patients, and report evidence of gingival fibromatosis associated with sensorineural hearing loss. Eligible study designs included case reports, case commentaries, and narrative reviews relevant to Jones syndrome with oral involvement.

The search was limited to studies published up to August 2025.

The primary focus of the studies was to compare diagnostic accuracy between genetic testing and clinical evaluation.

Studies were excluded if full-text access was unavailable; if clinical data were incomplete or lacked reference to the oral manifestations of Jones syndrome; if they analyzed patients presenting only with gingival fibromatosis without sensorineural hearing loss (or vice versa); or if they investigated other forms of gingival fibromatosis not related to Jones syndrome.

Search Strategy

A digital search was conducted across multiple databases (PubMed, Cochrane Library, Google Scholar, Scopus, and Web of Science).

The electronic search syntax used in PubMed, Cochrane Library, Google Scholar, Scopus, and Web of Science was:

(“Jones syndrome”) AND (“gingival fibromatosis”) AND (“hearing loss”) in titles, abstracts, and keywords.

Additionally, the reference lists of the included articles were examined to identify additional studies that met the inclusion criteria of the present review.

Study Selection

All duplicate records were removed. Two reviewers (V.G. and V.V.) independently screened titles and abstracts against pre-established criteria to assess relevance. Articles lacking sufficient information or not meeting the inclusion criteria based on titles and abstracts were excluded. The remaining articles were retained for full-text assessment to determine eligibility. Any disagreements were resolved through consensus and, when necessary, with the intervention of a third reviewer (M.G.).

Data Extraction

Two reviewers independently extracted data from each included study. The following variables were collected: author and year of publication, study design, patient age and sex, oral manifestations, dental treatment, follow-up, genetic diagnosis, and extraoral manifestations, as summarized in Table 4. Any discrepancies were resolved through discussion with the third reviewer and by consensus.

The outcomes reported by the selected articles, particularly those involving gingival fibromatosis, sensorineural hearing loss, and nephropathy, varied by study focus; the main outcomes are summarized in Table 3.

Table 1. PICO framework for the present review.

Population	Patients with gingival fibromatosis associated with sensorineural hearing loss
Intervention	Diagnosis through REST gene analysis
Comparison	Genetic diagnosis versus clinical diagnosis
Outcomes	Etiologic confirmation; severity of gingival fibromatosis and sensorineural hearing loss; additional oral manifestations; additional extraoral manifestations

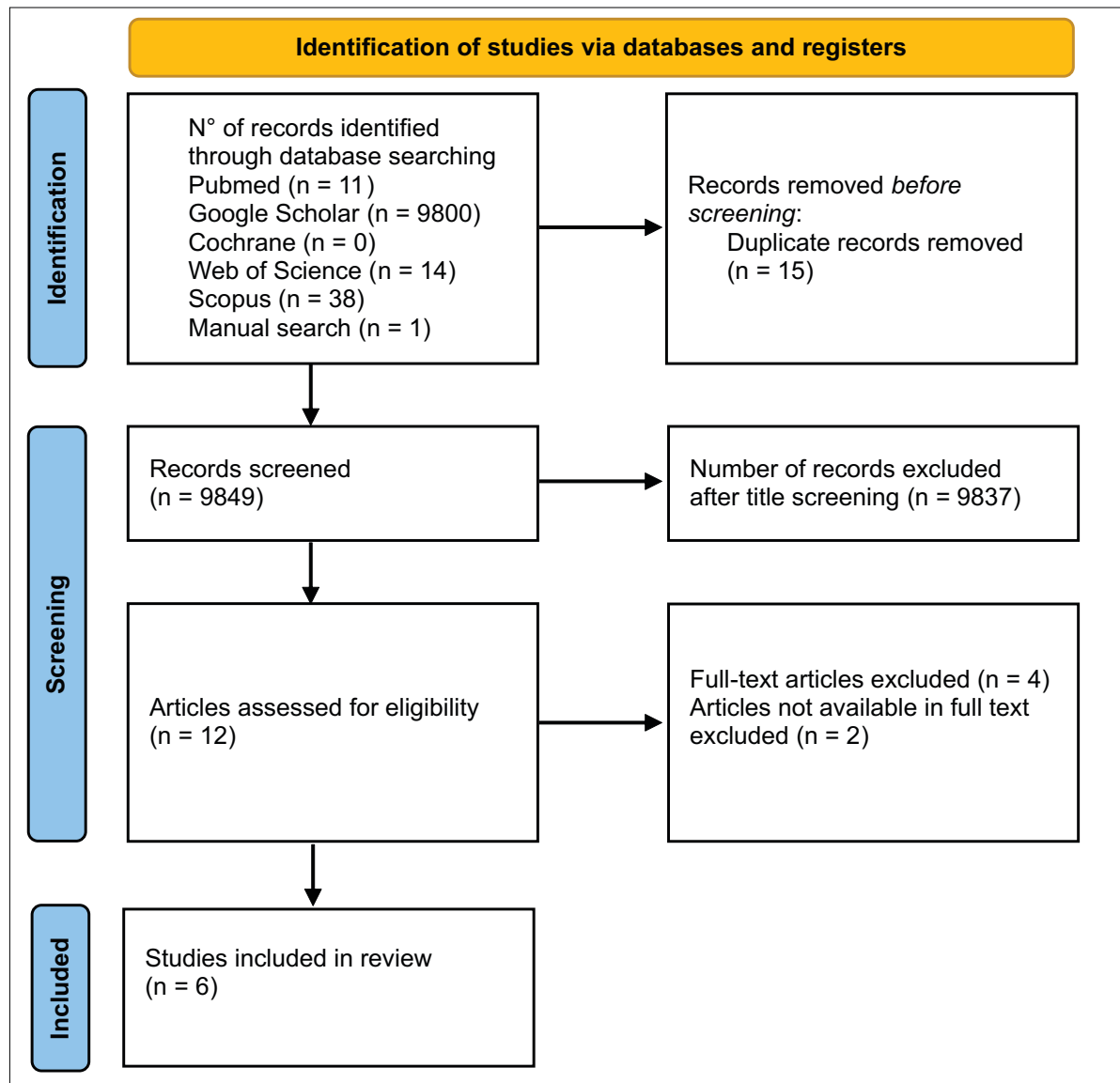


Figure 1. PRISMA flow diagram of study selection.

Table 2. Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
Studies published in English or Italian	Articles not accessible in full text
Studies involving young and/or adult patients	Studies with incomplete clinical data or lacking reference to oral manifestations of Jones syndrome
Studies reporting evidence of gingival fibromatosis associated with sensorineural hearing loss	Studies including patients with gingival fibromatosis without sensorineural hearing loss, or vice versa
Articles published in peer-reviewed scientific journals	Studies on forms of gingival fibromatosis unrelated to Jones syndrome

Risk of Bias

Two reviewers independently assessed the quality of the included studies.

Given the high prevalence of case reports in this review, which inherently carry a high risk of bias due to the absence of control groups, randomization, or

methods to minimize systematic errors, the Joanna Briggs Institute (JBI) checklist for case reports (6) was used to assess the risk of bias formally.

Applying this checklist (summarized in Table 5), the included studies demonstrated an overall moderate-to-high risk of bias.

Table 4. Summary of the main characteristics of the included studies.

Author	Year / Study Type	Patients / Age / Sex	Oral Manifestations	Dental Treatment	Follow-up	Genetic Diagnosis	Audiological Findings	Extraoral Manifestations
Hart-sfield et al.	1985 / Case report	4 (father, daughter, father's brother, paternal grandfather) / 33 and 10 years; ages of father's brother and grandfather not reported	Marked gingival fibromatosis; mild/moderate bone loss around incisors and molars; generalized gingival hyperplasia covering most of the anatomical crowns; delayed eruption of permanent incisors and first molars; midline palatal torus. Similar clinical picture Reported for deceased grandfather	No treatment reported	Not reported	Not available	Mild hearing loss; moderate hearing loss; moderate hearing loss	Hirsutism (father's brother)
Gita et al.	2014 / Case report	1 / 14 years / M	Generalized gingival fibromatosis, firm nodular fibrotic consistency, delayed eruption	Quadrant gingivectomy	Periodic review every 3 months; followed for 24 months (mild recurrence)	Not available	Progressive hearing loss	Not reported
Roopa et al.	2016 / Case report	1 / 15 years / M	Generalized gingival fibromatosis covering entire dental crowns, chewing difficulties	Scaling and root planing (no improvement after 1 month) followed by gingivectomy	Follow-up at 1–3–6 months: no recurrence	Not performed	Progressive hearing loss	Not reported
Aniyan et al.	2021 / Case report	1 / 27 years / M; positive family history	Generalized gingival fibromatosis almost completely covering upper incisors, bleeding pockets on probing	Incisional biopsy for diagnostic confirmation (dense fibrosis with perivascular inflammation); planned surgical gingivectomy	Long-term follow-up not reported	Not performed	Progressive sensorineural hearing loss for 7 years before presentation; use of hearing aid	Not reported
Rahikola et al.	2023 / Review	3 (father and two daughters) / F 11 years; F 14 years; M 42 years	Gingival fibromatosis causing delayed eruption of permanent teeth; generalized gingival fibromatosis and delayed eruption of Permanent teeth	Extraction of deciduous teeth and gingivectomy (daughters); gingivectomy at 20 years (father)	Follow-up reported for the father: no recurrence	c.2670_2673del; p.(Glu-891Profs*6)	Mild bilateral high-frequency SNHL; mild bilateral high-frequency SNHL; bilateral high-frequency SNHL at 5 years, Bilateral mid- and high-frequency SNHL at 40 years	F 11: hypertrichosis, hypertelorism; F 14: hypertrichosis; father: hypertrichosis, inguinal hernia

Table 5. Risk of bias assessment of included studies according to the JBI checklist for case reports

Study (year)	Patient clearly described	Complete clinical history	Diagnosis well substantiated	Intervention adequately described	Outcome clearly reported	Adequate follow-up	Supporting evidence	Discussion of limitations/alternatives	Overall judgement
Gita et al.	Yes	Partial	Yes	Yes	Yes, narrative	Short	Yes (clinical photographs)	Limited	Moderate risk
Lodato et al.	Yes	Yes	Yes + REST genetic analysis	Yes	Yes	Good	Yes	Present	Moderate–low risk
Rahikkala et al.	Yes	Yes	Yes + REST genetic analysis	Yes	Yes	Variable	Yes (genetic reports)	Present	Moderate–low risk
Roopa et al.	Yes	Partial	Yes	Yes	Yes, narrative	Short	Yes	Limited	Moderate–high risk
Hartsfield et al.	Yes	Yes	Yes	Yes	Yes	Short	Yes (clinical descriptions)	Limited	Moderate risk
Aniyan et al.	Yes	Yes	Yes	Yes	Yes	No	Yes	Limited	Moderate–high risk

Results

The electronic and manual search identified 9,864 records. After removal of duplicates ($n = 15$) and title screening, 9,837 articles were excluded as incompatible with the main aim of this review, leaving 12 articles eligible for abstract and full-text review. In the latter exclusion process, the discarded articles were: articles not available in full text ($n=2$) and articles analyzed clinically for a different syndrome. Following abstract and full-text assessments, four additional articles were excluded, leaving six studies included in this review.

The included studies comprised four case reports without genetic analysis (Aniyan et al. (7); Gita et al. (8); Roopa et al. (9); Hartsfield et al. (10)) and two studies including REST gene analysis documenting familial co-segregation (Rahikkala et al. (3); Lodato et al. (4)).

Rahikkala et al. (3) reported a father and his two daughters with gingival fibromatosis accompanied by sensorineural hearing loss. In the daughters, gingival fibromatosis caused delayed eruption of permanent teeth. Genetic analysis identified a mutation in the REST gene (c.2670_2673del, p.(Glu891Profs*6), exon 5) with familial co-segregation, providing an integrative review of the Jones syndrome phenotype and clinical recommendations.

Lodato et al. (6) described an Italian family in which both the proband and the mother were affected. Genetic analysis identified a REST mutation c.2645T>G p.(Leu882) (exon 5), present only in affected individuals and absent in two clinically healthy siblings.

The remaining studies reported Jones syndrome cases based solely on clinical analysis of oral and extraoral manifestations.

Hartsfield et al. (1985) (10) presented the second description of a family with autosomal dominant gingival fibromatosis and SNHL, contributing to the clinical delineation of the syndrome but without genetic testing.

Gita et al. (2014) (8) reported a male adolescent with generalized gingival fibromatosis and moderate-to-severe SNHL treated with quadrant gingivectomy and followed for 24 months, showing mild recurrence but no genetic analysis.

Roopa et al. (2016) (9) described a 15-year-old male with gingival fibromatosis and progressive hearing loss combined with alveolar bone loss, treated with gingivectomy and showing no recurrence at 6 months; a diagnosis of Jones syndrome was made clinically without genetic testing.

Aniyan et al. (7) reported an adult with familial gingival fibromatosis and SNHL managed with hearing aids; although more recent, this case also defined Jones syndrome clinically without clarifying the underlying genetics.

Discussion

Before the advent of genetic testing, the nosological attribution of "Jones syndrome" was based on the coexistence of gingival fibromatosis and sensorineural hearing loss (1) and, whenever possible, on familial co-segregation of these two features. As reported by

Hartsfield et al. (10), this approach inevitably leads to diagnostic uncertainty because gingival fibromatosis is highly heterogeneous: it can be isolated, syndromic, or drug-induced, while SNHL is common and multifactorial, and various syndromes may partially mimic the phenotype. In this context, clinical assessment alone could result in misclassification and did not allow a clear distinction between Jones syndrome, isolated gingival fibromatosis, or non-syndromic SNHL.

Genetic analysis of the REST gene significantly increases diagnostic accuracy. In the families reported by Rahikkala et al. (3) (frameshift mutation, exon 5) and Lodato et al. (4) (nonsense mutation, exon 5), the variant was present in affected individuals and absent in unaffected relatives, confirming Jones syndrome as a monogenic, REST-dependent entity. Both variants are truncating mutations in exon 5 (the last exon) (2) and are consistent with the proposed mechanism of loss-of-function/dominant-negative effect on REST transcriptional repression. This evidence defines a characteristic molecular profile of Jones syndrome, improving etiological attribution compared with clinical assessment alone.

As highlighted in this review, REST genetic analysis enhances diagnostic precision by confirming Jones syndrome and distinguishing it from atypical clinical variants, isolated gingival fibromatosis, and non-syndromic forms of SNHL.

Beyond diagnostic accuracy, the review also reveals practical clinical implications that cannot be achieved with clinical evaluation alone. Identification of the autosomal dominant inheritance pattern and the familial variant allows at-risk relatives to be tested, clarifies intra-familial penetrance, and supports targeted monitoring, such as audiometric evaluation in asymptomatic carriers, particularly during adolescence, when high-frequency SNHL may initially escape routine clinical screening. Such early interventions are justified only by molecular confirmation and cannot be reliably based on unconfirmed clinical cases.

Although molecular diagnosis does not change the indication for surgical treatment, it helps set realistic expectations and underscores the importance of oral hygiene and follow-up care. Germline REST mutations have also been associated with Wilms tumor predisposition (10). Both Lodato et al. (4) and Rahikkala et al. (3) reported no tumors in the respective families, but awareness of the genetic variant facilitates balanced counseling on potential, albeit unproven, extraoral risks.

In conclusion, genetic confirmation does not alter the periodontal-surgical procedure itself. Still, it significantly changes patient and family management by enabling early and targeted audiological surveillance, counseling, predictive testing, and precise differential diagnosis. This added value cannot be achieved through clinical diagnosis alone.

Conclusions

Within the limitations of this study, the following conclusions can be drawn:

1. The introduction of genetic testing has provided a

significant advancement in the scientific literature. The studies by Rahikkala et al. (2023) (3) and Lodato et al. (2025) (4) unequivocally demonstrated that truncating mutations in exon 5 of the REST gene are the cause of Jones syndrome. This finding provided the missing key, allowing definitive confirmation of the diagnosis, distinguishing Jones syndrome from phenotypically similar conditions such as isolated gingival fibromatosis, other syndromes with gingival fibromatosis, and non-syndromic REST-related hearing loss, and improving the understanding of the molecular mechanisms underlying the disease.

2. Genetic analysis enables accurate family counseling, identification of carriers before symptom onset, guidance for early audiological follow-up, and strengthens multidisciplinary patient management. Most importantly, it prevents misdiagnosis and inappropriate treatments, promoting a personalized approach.

In conclusion, this review demonstrates that REST gene analysis is now an indispensable tool, as it completes the diagnostic pathway, increases accuracy, and opens new perspectives for care and support of patients with Jones syndrome.

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Institutional Review Board Statement

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Informed Consent Statement

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Data Availability Statement

No new data were created or analyzed in this study. Data sharing does not apply to this article.

Conflicts of Interest

The authors declare no conflicts of interest

Abbreviations

The following abbreviations are used in this manuscript:
REST Repressor Element 1 Silencing Transcription Factor

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SNHL sensorineural hearing loss

PICO Population, Intervention, Comparison, Outcomes

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