

GENOMICS IN ORAL SUBMUCOUS FIBROSIS: A SCOPING REVIEW

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ABSTRACT

Background: Oral submucous fibrosis (OSMF) is a chronic, progressive, potentially malignant oral disorder strongly associated with areca-nut exposure. Although exposure-related mechanisms are well recognised, genetic and epigenetic variation may help explain differences in susceptibility, fibrosis severity, and malignant potential. **Objective:** To map the available evidence on genomic and molecular mechanisms implicated in OSMF, with emphasis on genetic susceptibility, extracellular-matrix regulation, epigenetic alterations, non-coding RNAs, and progression toward oral squamous cell carcinoma. **Methods:** This review is organised using a scoping-review framework. Relevant literature domains include genetic association studies, gene-expression investigations, epigenomic studies, non-coding-RNA research, and reviews of OSMF pathogenesis. PubMed/MEDLINE, Scopus, Web of Science, and Embase are proposed as the principal databases, with Google Scholar and reference-list screening as supplementary methods. The final manuscript should report the actual search dates, record counts, and study-selection figures after the searches are run and documented. **Results:** Published evidence implicates variants in xenobiotic-metabolism, antioxidant-defence, inflammatory, DNA-repair, and matrix-remodelling pathways. Epigenomic studies have identified DNA-methylation changes, while microRNA research suggests altered regulation of fibrosis-associated genes and signalling pathways. However, studies vary in population, sample size, methods, and outcome definitions, and many findings have not been independently replicated. **Conclusion:** Genomic research offers a useful framework for understanding inter-individual differences in OSMF, but current evidence is not sufficiently standardised for routine genetic risk prediction. Larger, well-characterised, multi-ethnic longitudinal studies integrating exposure history, genomic data, transcriptomics, epigenomics, and clinical outcomes are needed.

KEYWORDS: oral submucous fibrosis; genomics; genetic polymorphism; epigenetics; microRNA; fibrosis; malignant transformation.

INTRODUCTION

Oral submucous fibrosis (OSMF) is a chronic, progressive fibro-inflammatory disorder of the oral mucosa and a recognised oral potentially malignant disorder. Clinically, it may present with burning sensation, mucosal blanching, palpable fibrous bands, reduced mouth opening, and impaired tongue mobility. Areca-nut use, often in combination with betel quid, tobacco, or other additives, is the principal established exposure associated with the disease. OSMF remains an important public-health concern in South and Southeast Asia, where areca-nut products are widely consumed.^{1, 2}

The pathogenesis of OSMF is multifactorial. Areca-nut alkaloids and other constituents can influence fibroblast activity, oxidative stress, inflammatory signalling, collagen synthesis, and extracellular-matrix turnover. Increased collagen deposition together with reduced collagen degradation contributes to progressive tissue stiffness and fibrosis. Transforming growth factor-beta (TGF- β)-related signalling and other profibrotic pathways are frequently discussed in this process.²

Exposure alone does not fully explain the variability in disease occurrence, severity, or progression. Differences in genetic background, metabolism of areca-nut constituents, antioxidant capacity, inflammatory responses, and DNA repair may modify individual susceptibility. In parallel, epigenetic mechanisms—including DNA methylation, histone modification, and non-coding RNA regulation—may alter gene expression without changing the underlying DNA sequence.³⁻⁵

Genomic and molecular studies of OSMF have expanded, but the evidence is heterogeneous and distributed across candidate-gene studies, molecular profiling, and narrative or systematic reviews. A scoping review is therefore useful for mapping the main research areas, summarising recurring findings, and identifying methodological gaps without assuming that all available studies can be pooled quantitatively.

AIM AND OBJECTIVES

The aim of this scoping review is to map current evidence on genomic and molecular mechanisms associated with OSMF.

To describe reported genetic variants associated with susceptibility to OSMF.
To summarise molecular pathways involved in inflammation, oxidative stress, collagen accumulation, and extracellular-matrix remodelling.
To review evidence on epigenetic regulation and non-coding RNAs in OSMF.
To examine genomic and molecular findings relevant to malignant transformation.
To identify evidence gaps and priorities for future translational research.

MATERIALS AND METHODS

Study design and reporting framework

This manuscript follows the conceptual approach of a scoping review, intended to map the breadth and nature of evidence rather than estimate a single pooled effect. Reporting should be aligned with the PRISMA Extension for Scoping Reviews (PRISMA-ScR).^{1,2} Before submission, the completed search and selection process should be checked against the PRISMA-ScR checklist.

Information sources and search strategy

The planned electronic sources are PubMed/MEDLINE, Scopus, Web of Science, and Embase. Google Scholar may be used as a supplementary source, and the reference lists of relevant primary studies and reviews should be screened for additional records. Search terms should combine disease terminology with genomic and molecular concepts. An example search string is:

("oral submucous fibrosis" OR "oral submucous fibroses" OR OSMF OR OSF) AND (genomics OR genetic OR polymorphism OR "gene expression" OR epigenetics OR "DNA methylation" OR microRNA OR "non-coding RNA" OR fibrosis OR "molecular pathway")

The search string should be adapted to the syntax and controlled vocabulary of each database. The final report must state the date each database was searched, the publication period covered, any language restrictions, and the number of records retrieved. Because these operational details must reflect the searches actually completed, no database-specific hit counts or PRISMA flow numbers are invented in this draft.

Eligibility criteria

Eligible evidence includes human or laboratory studies investigating genetic variants, gene expression, DNA methylation, epigenetic regulation, microRNAs or other non-coding RNAs, molecular signalling, extracellular-matrix regulation, or molecular markers associated with OSMF susceptibility, severity, progression, or malignant transformation. Relevant observational and molecular studies were considered within the intended scope; reviews may be used to contextualise the field and identify primary studies.

Records should be excluded when they do not address OSMF or its genomic/molecular mechanisms, are unrelated to the review questions, or contain insufficient information for meaningful charting. Duplicate records should be removed before screening. Any restrictions on language, publication type, or date must be declared explicitly in the final version.

Study selection and data charting

After retrieval, titles and abstracts should be screened against the eligibility criteria, followed by full-text assessment of potentially relevant records. Reasons for full-text exclusion should be recorded. A PRISMA-ScR flow diagram should report the actual numbers identified, deduplicated, screened, assessed in full text, excluded, and included.

Data charting should capture author and year, country or population, study design, sample size, molecular method, gene or molecular marker, principal findings, and relevance to OSMF susceptibility, fibrosis, or malignant transformation. Findings can then be grouped thematically into genetic susceptibility, oxidative stress and inflammation, matrix remodelling, epigenetic regulation, non-coding RNAs, and malignant transformation.

Synthesis

A descriptive and thematic synthesis is appropriate given the diversity of study designs, populations, markers, and outcome measures. The review does not attempt a pooled meta-analysis. The strength and consistency of evidence should be interpreted cautiously, particularly where results derive from small candidate-gene studies or lack independent replication.

RESULTS

Research on OSMF genomics can be broadly grouped into candidate-gene association studies, investigations of profibrotic and inflammatory pathways, epigenomic profiling, and studies of microRNAs and other regulatory molecules. Reviews have highlighted the biological plausibility of gene–environment interactions in OSMF, but also the limited consistency between individual genetic-association findings.^{3–5} A final scoping review should insert the verified number of included records and summarise the study designs and populations identified by the completed search.

Genetic susceptibility and candidate-gene studies

Candidate-gene studies have examined variants in pathways related to xenobiotic metabolism, antioxidant defence, inflammatory signalling, DNA repair, and extracellular-matrix turnover. These pathways are biologically relevant because areca-nut exposure can generate oxidative stress and tissue injury, while host metabolic and inflammatory responses may influence the magnitude and duration of those effects.

A systematic review and meta-analysis published in 2026 assessed single-nucleotide polymorphisms reported in OSMF and identified associations in selected variants and genes, including GSTM1, GSTT1, MMP3, XRCC3, and CYP1A1.⁵ These findings are consistent with possible roles for detoxification, oxidative-stress handling, DNA repair, and matrix remodelling. Nevertheless, genetic associations should not be interpreted as definitive causal effects: differences in ancestry, exposure patterns, sample size, genotyping methods, and control selection may contribute to inconsistent results.

Inflammatory genes have also been investigated. A study of tumour necrosis factor- α (TNF- α) polymorphism reported an association with OSMF risk, suggesting that host inflammatory responses may contribute to disease susceptibility.⁶ However, cytokine activity is influenced by multiple genetic and environmental factors, and replication in independent populations is necessary before any variant can be considered a reliable clinical marker.

Profibrotic signalling and extracellular-matrix remodelling

Progressive fibrosis is a defining feature of OSMF. Areca-nut-associated cellular stress and inflammatory mediators can promote fibroblast activation and collagen accumulation. TGF- β signalling is particularly relevant because it regulates extracellular-matrix production and fibroblast phenotype. The balance between collagen synthesis and degradation is affected by matrix metalloproteinases (MMPs), their inhibitors, and other regulatory proteins.^{2, 3}

Genetic variation in profibrotic pathways has been explored, although not all studies have found frequent or consistent associations. For example, work examining TGF- β 1 polymorphisms in OSMF reported that variants were present at selected loci but were infrequent, illustrating the difficulty of attributing a complex phenotype to a small number of candidate variants.⁷ Matrix-related genes remain of interest because they may link inherited susceptibility with the tissue-level phenotype of persistent collagen deposition and reduced mucosal elasticity.

Oxidative stress, detoxification, and DNA repair

Areca-nut constituents may contribute to oxidative stress and cellular injury. Genes involved in glutathione-dependent detoxification, xenobiotic metabolism, and repair of DNA damage are therefore plausible susceptibility candidates. Reported associations involving GSTM1, GSTT1, CYP1A1, and XRCC3 suggest that detoxification capacity and DNA-repair pathways merit further investigation.⁵

However, the presence of a candidate-gene association does not establish that a variant independently predicts OSMF. Gene–environment interactions are likely to be important, and exposure assessment should distinguish frequency, duration, product composition, and co-use of tobacco or other substances. Future studies should use adequately powered designs and prespecified analyses to reduce false-positive findings.

Epigenetic alterations

Epigenetic mechanisms regulate gene expression without changing the nucleotide sequence. DNA methylation is one such mechanism and may be influenced by chronic exposure, inflammation, and cellular stress. A genome-wide DNA-methylation study of OSMF reported differentially methylated regions and candidate genes, including FGF13, RPS6KA3, and ACSL4, and described changes involving XIST.⁸ Such findings indicate that epigenomic alterations may contribute to the disease phenotype and may provide candidate markers for future validation.

Epigenetic results require careful interpretation. Differences in cell composition between fibrotic tissue and control mucosa, disease stage, exposure history, and laboratory platforms may influence observed methylation patterns. Cross-sectional results cannot determine whether an epigenetic change initiates fibrosis, results from chronic disease, or reflects both processes. Validation in independent cohorts and in relevant cell populations is essential.

MicroRNAs and other non-coding RNAs

MicroRNAs (miRNAs) regulate gene expression post-transcriptionally and can influence inflammation, cell proliferation, apoptosis, and extracellular-matrix pathways. Reviews of miRNA research in OSMF have described altered expression of regulatory miRNAs and their potential relationship to fibrotic signalling.⁹ A subsequent comprehensive analysis explored miRNAs and their target genes in OSMF, supporting the relevance of regulatory RNA networks to disease biology.¹⁰

Non-coding RNA findings are promising but remain exploratory. Studies may differ in specimen type, RNA extraction, normalisation strategy, disease stage, and choice of control tissue. Candidate miRNAs should be validated using independent samples and transparent laboratory methods. Their potential utility as minimally invasive biomarkers also requires assessment of stability, diagnostic accuracy, and added value over clinical examination and established risk factors.

Genomics and malignant transformation

OSMF is a potentially malignant disorder, and a subset of affected individuals develop oral squamous cell carcinoma. Molecular changes related to chronic inflammation, oxidative stress, altered DNA repair, epigenetic dysregulation, and changes in cell-cycle control may contribute to progression.¹⁻³ Genomic research could help distinguish pathways associated with fibrosis alone from those associated with epithelial dysplasia or malignant transformation.

At present, no single genomic marker can reliably replace clinical assessment, histopathological evaluation when indicated, and long-term surveillance. Studies of malignant transformation should use longitudinal designs, clearly defined outcomes, and adequate follow-up. They should also account for continued areca-nut exposure, tobacco use, alcohol exposure where relevant, and other clinical risk factors.

Potential clinical implications

Genomic and epigenomic findings may eventually help characterise biological heterogeneity, identify pathways for therapeutic investigation, and support risk stratification. However, clinical translation requires evidence of reproducibility, analytical validity, clinical validity, and meaningful benefit to patient care. No genetic test should be presented as clinically validated for routine OSMF screening or prediction on the basis of the current evidence summarised here.

DISCUSSION

This review maps several connected areas of OSMF research: inherited susceptibility, oxidative stress and detoxification, inflammatory signalling, extracellular-matrix remodelling, epigenetic regulation, and non-coding RNA networks. Together, these findings support a multifactorial model in which environmental exposure interacts with host biology to influence the development and progression of fibrosis.³⁻⁵

The candidate-gene literature provides plausible leads, especially in pathways related to detoxification, DNA repair, inflammation, and matrix turnover. Yet the evidence remains vulnerable to small sample sizes, population stratification, inconsistent exposure measurement, multiple testing, and selective publication. The presence of statistically significant associations in individual studies should therefore be distinguished from replicated and clinically useful prediction.

Epigenomic and miRNA investigations broaden the field beyond fixed DNA sequence variation. They may capture molecular responses to chronic exposure and tissue remodelling, but causal direction is often unclear. Prospective sampling, paired tissue and blood or saliva specimens where appropriate, and integration of genomic with transcriptomic and clinical data could help determine which changes precede disease progression and which are consequences of established fibrosis.

Research would benefit from harmonised diagnostic criteria, clear reporting of areca-nut product and exposure history, representative control groups, adequate statistical power, correction for multiple comparisons, and independent validation. Multi-centre cohorts from different regions are particularly important because genetic ancestry, product composition, and exposure practices vary. Studies investigating malignant transformation should prioritise longitudinal follow-up and clinically meaningful endpoints.

LIMITATIONS

This manuscript is a thematic synthesis of selected published evidence and is intended as a scoping-review draft. The database search dates, database-specific retrieval counts, duplicate-removal totals, screening decisions, and final included-study count have not been independently verified in this document. Consequently, it should not be described as a completed systematic database search until those steps are carried out and documented. In addition, the underlying literature is heterogeneous, and findings from candidate-gene studies may be affected by limited sample sizes, inconsistent methods, and incomplete replication.

CONCLUSION

Genomic and molecular research suggests that OSMF arises through interactions between areca-nut-associated exposures and host biological pathways involving detoxification, oxidative stress, inflammation, DNA repair, extracellular-matrix remodelling, epigenetic regulation, and non-coding RNAs. Although these findings provide a valuable framework for understanding disease heterogeneity, current evidence does not support routine genomic testing for OSMF risk prediction. Future research should emphasise large and diverse cohorts, rigorous exposure assessment, independent validation, and longitudinal evaluation of clinically relevant outcomes, particularly malignant transformation.

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