# GENE REARRANGEMENTS IN PAROTID TUMORS: ROLE OF PLAG1, HMGA2, AND MAML2 FUSIONS IN DIAGNOSTIC AND PROGNOSTIC STRATIFICATION

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## Abstract

Parotid gland tumors exhibit marked morphological and molecular heterogeneity, requiring increasingly integrated diagnostic and prognostic approaches. This study consisted of a systematic review of the

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literature addressing the prognostic impact of gene rearrangements involving PLAG1, HMGA2, and MAML2 in salivary gland neoplasms. The search strategy included major international databases, prioritizing studies published between 2021 and 2025, with inclusion criteria focused on molecular investigations presenting clinicopathological correlations. The findings demonstrated that, in pleomorphic adenoma, PLAG1 and HMGA2 fusions primarily act as early tumorigenic events and are generally associated with indolent clinical behavior. However, specific fusion variants and additional genetic alterations may indicate an increased risk of progression to carcinoma ex pleomorphic adenoma. In mucoepidermoid carcinoma, MAML2 rearrangement showed a more consistent association with favorable prognosis, including lower recurrence rates and improved overall survival. The clinical relevance of these molecular markers is supported by the WHO Classification of Tumours, which incorporates molecular criteria into the classification of salivary gland tumors. In conclusion, the prognostic value of gene fusions is context-dependent and should be interpreted alongside histopathological and clinical parameters. The consolidation of precision medicine in parotid tumors requires prospective multicenter studies to validate predictive models based on integrated molecular data.

***Keywords:*** Gene fusions, Mucoepidermoid carcinoma, Pleomorphic adenoma, Precision medicine, Prognosis.

## INTRODUCTION

Parotid gland tumors represent the most prevalent group among salivary gland neoplasms and are characterized by substantial morphological, immunophenotypic, and genetic heterogeneity. This diversity imposes significant diagnostic challenges, especially in small or incipient samples, predominantly cystic lesions, or tumors with extensive areas of metaplasia, in which classic histological criteria may not be fully evident. The contemporary classification of head and neck neoplasms recognizes that several salivary entities are defined by specific molecular alterations, particularly chromosomal translocations and recurrent gene fusions (Who Classification Of Tumours Editorial Board, 2022). In this context,

rearrangements involving the genes PLAG1, HMGA2, and MAML2 play a central role in the diagnostic and prognostic stratification of parotid tumors.

From a clinical perspective, these neoplasms often present as a progressively enlarging mass in the parotid region, which may or may not be associated with pain, facial paresis, or inflammatory signs. Correlation between physical examination and imaging methods is fundamental for diagnostic planning, as illustrated in Figure 1, which demonstrates a parotid-region swelling associated with a solid mass identified on computed tomography.

Historically, the diagnosis of these neoplasms was based predominantly on morphological analysis in conjunction with immunohistochemistry. However, overlap of architectural patterns among benign and malignant tumors—such as pleomorphic adenoma, myoepithelial tumors, and low-grade carcinomas—may compromise diagnostic reproducibility (Toper e Sarioğlu, 2021). The incorporation of molecular pathology has enabled more refined classification by demonstrating that many salivary tumors harbor specific genetic drivers that sustain tumorigenesis (Stenman et al., 2022). In addition, the genetic heterogeneity of these lesions has direct implications for clinical behavior and the possibility of malignant transformation (Yousaf et al., 2022).

Pleomorphic adenoma, the most frequent benign parotid neoplasm, has as foundational molecular events the rearrangements involving PLAG1 and HMGA2. Chromosomal translocations lead to overexpression of these genes through activation by heterologous promoters, resulting in sustained proliferative stimulation (Stenman et al., 2022). Recent transcriptomic analyses have demonstrated that the gene fusion landscape in these tumors is largely dominated by alterations involving PLAG1, reinforcing its central role in salivary tumor biology (Afshari _et al., _2025). Identification of these fusions has high diagnostic specificity and aids in distinguishing pleomorphic adenoma from other neoplasms with similar morphology.

The diagnostic utility of these genes is reinforced by immunohistochemical studies. A high frequency of HMGA2 expression has been observed in pleomorphic adenomas, demonstrating its

applicability as an ancillary marker, particularly in cases with atypical morphology (Owosho et al., 2022). Similarly, the combined evaluation of PLAG1 and HMGA2 in minor salivary gland tumors contributes to greater diagnostic confidence in challenging situations (Barca et al., 2021). In predominantly cystic parotid neoplasms, in which the differential diagnosis includes multiple benign and malignant entities, molecular studies can be decisive to avoid underdiagnosis or incorrect classification (Ribeiro e Maleki, 2022).

Genotype–phenotype correlation has been progressively clarified in the literature. Certain rearrangements are associated with specific morphological patterns, suggesting direct influence on tumor architecture. HMGA2-WIF1 rearrangements have been described in a distinct subset of pleomorphic adenomas with prominent trabecular morphology, resembling canalicular adenoma (Agaimy et al., 2021). Neoplasms harboring the TGFBR3-PLAG1 fusion have shown association with myoepithelial differentiation and evidence of high-grade transformation, indicating possible prognostic impact (Rupp et al., 2021). Cases with MALAT1::PLAG1 fusion associated with exuberant squamous and mucinous metaplasia highlight potential diagnostic pitfalls when morphology deviates from the classic pattern (Wang et al., 2025). These findings reinforce that molecular characterization goes beyond confirmatory value, contributing to the understanding of tumor biological behavior.

Progression of pleomorphic adenoma to carcinoma ex pleomorphic adenoma is a clinically highly relevant event associated with worse prognosis. Alterations involving PLAG1 and HMGA2 have been implicated in acquisition of a malignant phenotype and in the genomic instability observed in such cases (De Lima-Souza et al., 2024). Thus, molecular investigation may assist in early identification of lesions with greater potential for transformation, guiding a more vigilant clinical approach.

Within the spectrum of malignant parotid neoplasms, mucoepidermoid carcinoma stands out due to its frequent association with MAML2 gene rearrangement, generally through the CRTC1::MAML2 fusion. This rearrangement is considered a characteristic molecular marker of the entity and has diagnostic and prognostic relevance (Bishop et al., 2022). Tumors with MAML2 rearrangement may

exhibit significant morphological variation, including the absence of evident squamoid cells, thereby expanding the recognized histological spectrum (Bishop et al., 2022). An association has been observed between the presence of the rearrangement, histological subtype, and anatomical location, suggesting an additional stratifying role (Kim et al., 2025). Variants involving YAP1::MAML2 further increase the molecular complexity of these neoplasms (Mijares et al., 2025).

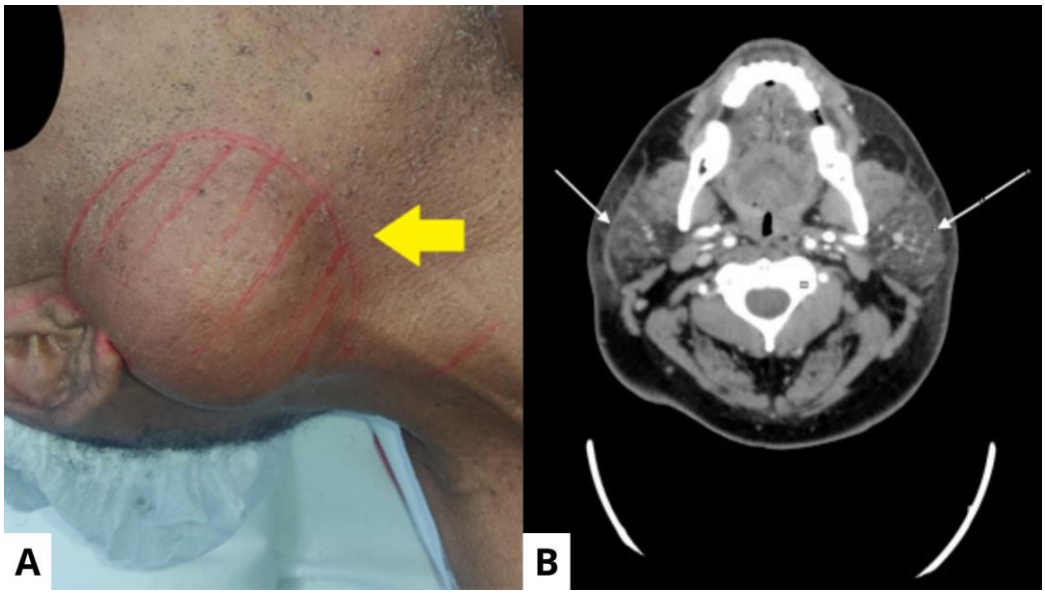
The consolidation of targeted RNA sequencing techniques has enabled sensitive and specific detection of these fusions in routine diagnostic practice. High effectiveness of RNA sequencing has been demonstrated for identifying fusion genes in salivary tumors, including in formalin-fixed, paraffin-embedded samples (Bubola et al., 2021). However, it should be emphasized that interpretation of molecular findings must be integrated with clinical and morphological data, considering possible rare variants and diagnostic pitfalls (Kaur et al., 2022).

International guidelines emphasize the importance of molecular characterization in the contemporary approach to salivary gland carcinomas, highlighting its role in therapeutic decision-making and clinical follow-up (European Society For Medical Oncology; Euracan, 2024). Integration of morphology, immunohistochemistry, and molecular genetics promotes greater classificatory precision and improved prognostic assessment.

Comparative studies also demonstrate that PLAG1 and HMGA2 rearrangements can be identified in cutaneous mixed tumors and myoepithelial tumors, suggesting biological continuity across different anatomical sites (Macagno et al., 2024; Mansour et al., 2024). This convergence reinforces the relevance of molecular signatures in defining neoplastic entities, often surpassing limitations imposed by morphology alone.

**Figure 1**

*Clinical representation of a patient with an enlarging mass in the parotid region associated with a CT image showing a solid mass in the parotid gland.*




Source: A) Nódulo em parótida: quando operar? (2020), B) Asistolia por compresión del seno carotídeo: una complicación potencialmente fatal de la parotiditis vírica (2014)

Given this panorama, it is observed that gene rearrangements involving PLAG1, HMGA2, and MAML2 constitute fundamental molecular markers in differentiating pleomorphic adenoma, mucoepidermoid carcinoma, and other parotid neoplasms, contributing to greater diagnostic accuracy, recognition of morphological variants, and identification of potential risks of malignant transformation.

Moreover, such alterations have relevant prognostic implications, especially in the context of high-grade transformation and risk stratification.

Accordingly, the present study aims to analyze the role of PLAG1, HMGA2, and MAML2 gene fusions in the diagnostic and prognostic stratification of parotid tumors, discussing their correlation with histopathological, immunohistochemical, and clinical aspects in light of recent scientific evidence.

## METHODOLOGY

The present study consists of a systematic literature review conducted with the objective of critically analyzing the role of gene rearrangements involving PLAG1, HMGA2, and MAML2 in the

diagnostic and prognostic stratification of parotid tumors. The review was structured according to international guidelines for the development of systematic reviews, encompassing definition of the guiding question, a standardized search strategy, explicit inclusion and exclusion criteria, a staged selection process, and qualitative analysis of findings.

The research question was formulated based on an adapted PICO strategy for diagnostic and prognostic studies, considering as the population patients with parotid tumors; as the exposure, the presence of gene rearrangements involving PLAG1, HMGA2, and/or MAML2; as the comparison, tumors classified solely by morphological criteria or without identification of these fusions; and as outcomes, impact on diagnostic accuracy and prognostic implications. The guiding question defined was: what is the role of PLAG1, HMGA2, and MAML2 gene fusions in the diagnostic and prognostic stratification of parotid tumors?

The bibliographic search was performed in PubMed/MEDLINE, Scopus, Web of Science, Embase, and SciELO databases, covering the period from 2021 to 2026 in order to capture up-to-date evidence regarding the molecular classification of salivary tumors. Controlled descriptors and free terms in English and Portuguese were used, combined with Boolean operators AND and OR. The main descriptors included: “Salivary gland tumors”, “Parotid neoplasms”, “Gene rearrangement”, “Gene fusion”, “PLAG1”, “HMGA2”, “MAML2”, “Mucoepidermoid carcinoma”, “Pleomorphic adenoma”, “Molecular pathology”, “Diagnosis”, and “Prognosis”. The search strategy was adapted to the specificities of each database. In addition, a manual search of the reference lists of selected articles was conducted to identify potentially relevant additional studies.

The review included original articles published in peer-reviewed scientific journals that addressed parotid tumors or major salivary gland tumors with specific analysis of PLAG1, HMGA2, and/or MAML2. Eligible studies investigated diagnostic aspects, prognostic aspects, or genotype–phenotype correlation, provided that they presented clearly described molecular methodology, including techniques such as fluorescence in situ hybridization (FISH), reverse transcription polymerase chain reaction (RT-

PCR), RNA sequencing, or other next-generation sequencing approaches. Articles published in English, Portuguese, or Spanish and involving human samples were accepted.

Excluded were isolated case reports without in-depth molecular analysis, editorials, letters to the editor, and conference abstracts without full text available. Studies exclusively experimental in vitro or in animal models were also excluded, as were works addressing tumors from other locations without clear discrimination of parotid cases. Articles that did not provide adequate methodological description or did not report diagnostic or prognostic outcomes were likewise disregarded.

The study selection process occurred in three stages. Initially, titles and abstracts were read, and those manifestly irrelevant to the topic were excluded. Next, full texts of potentially eligible studies were read, applying inclusion and exclusion criteria rigorously. Finally, studies fully meeting the established criteria were included in the final analysis. Any divergences in selection were resolved by consensus among reviewers, ensuring greater reliability of the process.

Data extraction was performed using a standardized form containing information regarding author and year of publication, country of origin, study design, number of cases analyzed, tumor histological subtype, molecular method used, type of rearrangement identified, main diagnostic findings, prognostic implications, and limitations reported by the authors. Data were systematically organized to enable comparative analysis among included studies.

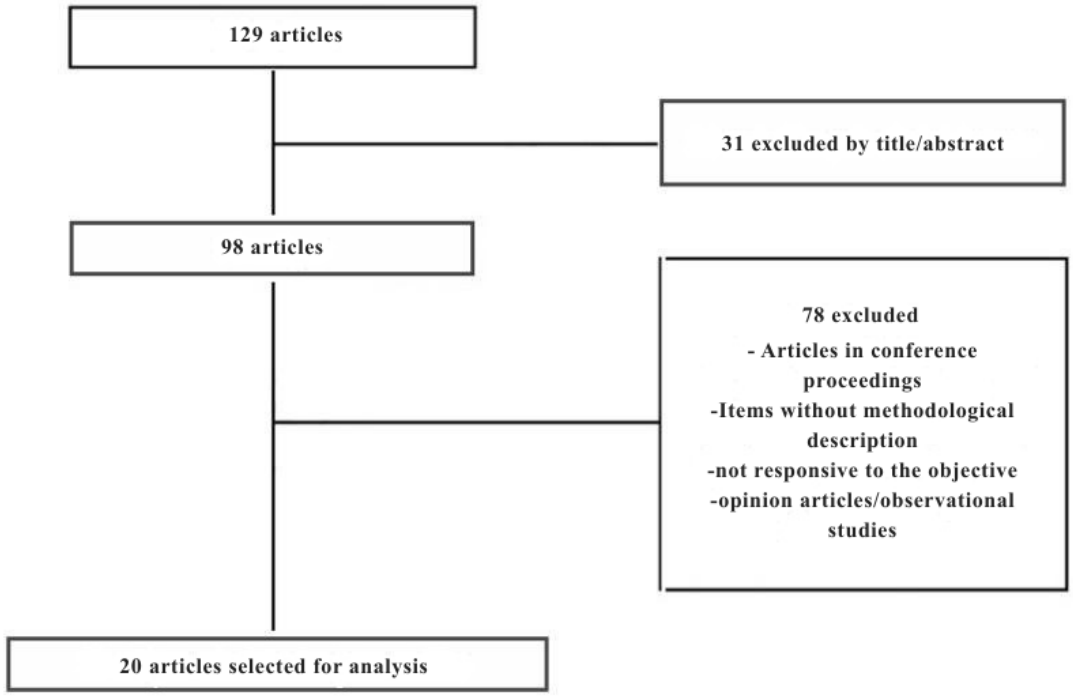
Methodological quality assessment of observational studies was conducted using an instrument adapted from the Newcastle–Ottawa scale, considering criteria related to sample selection, comparability between groups, and outcome assessment. In studies with a diagnostic focus, additional evaluation considered clarity of methodological description, adequacy of molecular techniques employed, and consistency of the diagnostic criteria used.

Data synthesis was performed qualitatively, considering methodological heterogeneity among studies, especially regarding methods for detecting gene fusions and the outcomes evaluated. The frequency of PLAG1, HMGA2, and MAML2 rearrangements in different tumor subtypes, correlation

between gene fusion and morphological pattern, association with histological grade and risk of malignant transformation, and the impact of these alterations on diagnostic accuracy and prognostic stratification were analyzed. Due to variability in study designs and lack of uniform quantitative data, no statistical meta-analysis was performed.

**Figure 2**

*Flowchart of the selection process of studies included in the systematic review!*




Source: Authors (2026)

As this study was based exclusively on secondary data from the scientific literature, submission to a Research Ethics Committee was not required. The adopted methodology sought to ensure scientific rigor, transparency, and reproducibility, enabling consistent critical analysis of the available evidence regarding the role of PLAG1, HMGA2, and MAML2 fusions in parotid tumors.

## RESULTS AND DISCUSSION

Understanding of gene rearrangements in parotid tumors has evolved significantly over the last decade, shifting from a strictly diagnostic approach toward an integrated perspective that incorporates prognostic and therapeutic implications. In the context of precision medicine, fusions such as PLAG1, HMGA2, and MAML2 began to be investigated not only as entity-defining markers, but also as potential modulators of tumor biological behavior.

As systematized by the WHO Classification of Tumours, incorporation of molecular criteria into the classification of salivary neoplasms reflects this paradigmatic transition.

Thus, the subitems below critically analyze the prognostic impact of these specific fusions, considering their correlation with histopathological characteristics, risk of malignant transformation, and clinical outcomes in light of the most recent evidence.

### GENE REARRANGEMENTS AS PRECISION MEDICINE TOOLS IN PAROTID TUMORS

Analysis of the selected studies investigated the molecular landscape of salivary gland tumors, with emphasis on parotid neoplasms and rearrangements involving PLAG1, HMGA2, and MAML2. Qualitative analysis of the data revealed consistency regarding the structuring role of these gene fusions in diagnostic redefinition, prognostic stratification, and consolidation of precision medicine.

In pleomorphic adenomas, there was a predominance of rearrangements involving PLAG1, recognized as initiating events in tumorigenesis. According to Stenman et al. (2022), chromosomal translocations that promote PLAG1 overexpression constitute a central molecular mechanism of the entity. Afshari et al. (2025), when analyzing the transcriptomic and gene fusion landscape, confirmed the molecular heterogeneity of pleomorphic adenomas, although with strong convergence toward PLAG1 activation.

HMGA2 expression was also frequently documented. Owosho et al. (2022) identified marked immunopositivity for HMGA2 associated with molecular rearrangements, suggesting complementary

diagnostic value. Barca et al. (2021) demonstrated that PLAG1 and HMGA2 participate in common molecular pathways in minor salivary gland tumors, reinforcing the relevance of these alterations across different anatomical contexts.

Specific morphological subgroups showed distinct genotypic correlation. Agaimy et al. (2021) identified HMGA2-WIF1 rearrangements in a subset with prominent trabecular morphology. Rupp et al. (2021) described TGFBR3-PLAG1 fusions associated with myoepithelial differentiation and evidence of high-grade transformation. In addition, De Lima-Souza et al. (2024) highlighted additional alterations in PLAG1 and HMGA2 associated with progression to carcinoma ex pleomorphic adenoma, suggesting prognostic implication.

In mucoepidermoid carcinoma, studies converged on the centrality of MAML2 rearrangement. Bishop et al. (2022) expanded the entity's histological spectrum by demonstrating that MAML2-rearranged tumors may lack evident squamous differentiation, constituting a diagnostic pitfall. Kim et al. (2025) demonstrated a significant association between MAML2 rearrangement, histological subtype, and anatomical location, reinforcing its utility in clinical stratification.

Rare cases also expand the molecular spectrum. Mijares et al. (2025) reported carcinoma with YAP1::MAML2 fusion in the parotid gland, indicating that MAML2 alterations are not restricted to classic mucoepidermoid carcinoma.

From a methodological standpoint, Bubola et al. (2021) demonstrated that targeted RNA sequencing enables efficient detection of multiple gene fusions in routine diagnostic workflows. However, Kaur et al. (2022) warned of potential interpretive pitfalls, emphasizing the need to integrate morphology with molecular data.

Formal incorporation of these markers is supported by international classification. The WHO Classification of Tumours Editorial Board (2022) recognized gene rearrangements as defining diagnostic criteria in several salivary neoplasms. Complementarily, the European Society for Medical Oncology;

EURACAN (2024) recommended integrating molecular tests into clinical management, especially in complex cases.

The main findings regarding pleomorphic adenomas are summarized in the table below.

**Table 1**

*Gene rearrangements in pleomorphic adenoma and clinical implications*

| **Rearrangement** | **Morphological association** | **Diagnostic implication** | **Prognostic implication** | **Author (year)** |
|---|---|---|---|---|
| PLAG1 (various fusions) | Classic pleomorphic adenoma | Diagnostic confirmation | Molecular basis of tumorigenesis | Stenman *et al.* (2022); Afshari *et al*. (2025) |
| HMGA2 | Frequent nuclear expression | Immunohistochemical support | Possible association with progression | Owosho *et al*. (2022); De Lima-Souza *et al*. (2024) |
| HMGA2-WIF1 | Trabecular morphology | Morphological subclassification | Characterization of a specific subgroup | Agaimy *et al*. (2021) |
| TGFBR3-PLAG1 | Myoepithelial differentiation | Molecular confirmation | Evidence of high grade in a subset | Rupp *et al*. (2021) |

Source: Authors (2026)

Findings regarding mucoepidermoid carcinoma and the clinical application of MAML2-related rearrangements are organized below

**Table 2**

*Rearrangements involving MAML2 and impact on precision medicine*

| Alteration | Diagnostic implication | Clinical application | Author (year) |
|---|---|---|---|
| MAML2 (classic) | Defines mucoepidermoid carcinoma | Improved histological stratification | Bishop *et al.* (2022); Kim *et al*. (2025) |
| YAP1::MAML2 | Expansion of the tumor spectrum | Recognition of rare variants | Mijares *et al*. (2025) |
| RNA sequencing | Simultaneous detection of fusions | Application in routine diagnostics | Bubola *et al.* (2021) |
| Molecular integration (WHO/ESMO) | Formal diagnostic criterion | Standardization and clinical management | WHO(2022); ESMO/EURACAN (2024) |

Source: Authors (2026)

Taken together, synthesis of the studies demonstrates that gene rearrangements constitute essential tools in precision medicine applied to parotid tumors. Identification of specific fusions increases diagnostic accuracy, enables more refined morphological subclassification, and provides relevant prognostic support. Convergence between histopathological and molecular data consolidates an integrated diagnostic model aligned with international guidelines and contemporary demands of personalized oncology.

## PROGNOSTIC IMPACT OF PLAG1, HMGA2, AND MAML2 FUSIONS

Systematic analysis of the literature demonstrated that gene fusions involving PLAG1, HMGA2, and MAML2 exert variable prognostic impact in parotid tumors, particularly in pleomorphic adenoma and mucoepidermoid carcinoma. Although these rearrangements are classically recognized as diagnostic markers, recent evidence indicates that they also play a relevant role in risk stratification, assessment of malignant transformation potential, and definition of clinical behavior.

In pleomorphic adenoma, PLAG1 fusions are considered initiating events in tumorigenesis. As emphasized by Stenman et al. (2022), PLAG1 activation by chromosomal translocations results in sustained overexpression without necessarily implying aggressive behavior.

Convergently, Afshari et al. (2025) highlighted that tumors harboring classic PLAG1 fusions maintain a transcriptomic profile compatible with an indolent clinical course.

However, the literature indicates that prognostic impact may vary according to the fusion partner. Rupp et al. (2021) identified cases with TGFBR3-PLAG1 rearrangement associated with prominent myoepithelial differentiation and, in specific subgroups, histological characteristics of greater aggressiveness. These findings suggest that the mere presence of PLAG1 should not be interpreted in isolation; rather, the full molecular context must be considered.

With respect to HMGA2, recent studies indicate an association with greater genomic instability and potential tumor progression. Owosho et al. (2022) observed that HMGA2 overexpression may reflect underlying structural alterations correlated with increased proliferative activity. Complementarily, De Lima-Souza et al. (2024) demonstrated that HMGA2 alterations, especially when coexisting with additional rearrangements, are implicated in transition to carcinoma ex pleomorphic adenoma.

The prognostic relevance of these alterations in pleomorphic adenoma is summarized below.

**Table 3**

*Prognostic impact of PLAG1 and HMGA2 fusions in pleomorphic adenoma*

| Fusion | Biological association | Prognostic impact | Author (year) |
|---|---|---|---|
| PLAG1 (classic) | Stable initiating event | Typical benign behavior | Stenman *et al*. (2022); Afshari *et al*. (2025) |
| TGFBR3-PLAG1 | Marked myoepithelial differentiation | Possible association with greater aggressiveness | Rupp *et al*. (2021) |
| HMGA2 | Nuclear overexpression | Potential correlation with progression | Owosho *et al*. (2022) |
| PLAG1/HMGA2 with additional alterations | Genomic instability | Association with carcinoma ex pleomorphic adenoma | De Lima-Souza *et al.* (2024) |

Source: Authors (2026)

In mucoepidermoid carcinoma, rearrangement involving MAML2 has a more consistently documented prognostic impact. As emphasized by Bishop et al. (2022), tumors positive for MAML2 fusion generally exhibit better overall survival and lower recurrence rates compared to negative cases.

Kim et al. (2025) corroborated these findings by demonstrating a significant association between MAML2 positivity and low- and intermediate-grade histological subtypes.

Incorporation of this evidence into international guidelines reinforces its clinical relevance. According to the WHO Classification of Tumours, MAML2 rearrangement constitutes a defining diagnostic criterion for mucoepidermoid carcinoma and is frequently associated with better clinical outcomes. Similarly, the European Society for Medical Oncology and EURACAN (2024) highlighted that MAML2 status may assist in therapeutic decision-making, especially in low-grade tumors.

However, the review also revealed relevant molecular heterogeneity. Kaur et al. (2022) emphasized that absence of MAML2 fusion does not, by itself, determine worse prognosis and should be interpreted in light of histological and clinical parameters. Furthermore, Mijares et al. (2025) described a

variant involving YAP1::MAML2 with distinct morphological characteristics, suggesting that different fusion partners may modify biological behavior.

The main findings regarding the prognostic impact of MAML2 fusions are presented below.

**Table 4**

*Prognostic impact of MAML2 fusions in mucoepidermoid carcinoma*

| Fusion | Clinical association | Prognostic implication | Author (year) |
|---|---|---|---|
| MAML2 (classic) | Low/intermediate grade | Better survival and lower recurrence | Bishop *et al.* (2022); Kim *et al*. (2025) |
| Ausência de MAML2 | Heterogeneous cases | Prognosis dependent on grade and stage | Kaur *et al*. (2022) |
| YAP1::MAML2 | Rare variant | Potentially distinct behavior | Mijares *et al*. (2025) |
| Recognition in guidelines | Formal diagnostic criterion | Support for therapeutic stratification | WHO (2022); ESMO/EURACAN (2024) |

Source: Authors (2026)

Overall, the findings of this systematic review indicate that the prognostic impact of PLAG1, HMGA2, and MAML2 fusions is dependent on histological context, the fusion partner, and the presence of additional genetic alterations. In pleomorphic adenomas, PLAG1 is predominantly associated with benign behavior, whereas complex or coexisting rearrangements may signal risk of transformation. In mucoepidermoid carcinoma, in turn, MAML2 positivity correlates more consistently with better prognosis.

These results reinforce that interpretation of gene rearrangements should occur in an integrated manner with morphological and clinical evaluation, consolidating precision medicine as an essential instrument in prognostic stratification of parotid tumors.

## CONCLUSION

This systematic review showed that gene rearrangements involving PLAG1, HMGA2, and MAML2 occupy a central position in the contemporary understanding of the molecular biology of parotid tumors. Initially recognized as entity-defining diagnostic markers, these events have also come to be interpreted from a prognostic standpoint, contributing to risk stratification and consolidation of precision medicine in salivary pathology. Incorporation of these markers into international classification, as established by the WHO Classification of Tumours, reinforces their clinical and scientific relevance.

In pleomorphic adenomas, fusions involving PLAG1 and HMGA2 demonstrated an impact predominantly associated with early tumorigenesis, with maintenance of benign behavior in most cases. However, the presence of specific fusion partners or additional genetic alterations may signal greater biological instability and risk of progression to carcinoma ex pleomorphic adenoma. Thus, the prognostic value of these fusions proves to be dependent on the broader molecular context, requiring integrated interpretation among morphology, genetic profile, and clinical data.

In mucoepidermoid carcinoma, fusion involving MAML2 showed a more consistent association with better prognosis, especially in low- and intermediate-grade tumors. Evidence indicates lower recurrence rates and improved overall survival in cases positive for this rearrangement, although absence of the fusion does not, in isolation, determine aggressive behavior. Therefore, the prognostic impact of MAML2 should be analyzed together with traditional histological criteria and clinical staging.

Across entities, the findings reinforce that interpretation of gene rearrangements should not occur in an isolated or deterministic manner. The genetic heterogeneity of salivary tumors imposes caution in extrapolating data, making integration among molecular findings, histopathological architecture, and clinical course essential. This integrative model represents a substantial advance over exclusively morphological approaches, enabling more individualized and potentially more effective therapeutic decisions.

Despite advances, gaps persist in the literature, especially regarding methodological standardization and scarcity of prospective analyses with long-term follow-up. Most available evidence derives from retrospective series and institutional cohorts, limiting generalizability. Furthermore, variability in molecular detection methods may influence interpretation of findings and comparison across studies.

In this scenario, development of a prospective multicenter study is suggested, with standardized molecular analysis by next-generation sequencing, integrating genomic, transcriptomic, and clinical data in longitudinal follow-up. Such an investigation would allow a more robust assessment of the independent prognostic impact of PLAG1, HMGA2, and MAML2 fusions, in addition to identifying potential interactions with other emerging genetic alterations. Consolidation of collaborative databases may contribute to building more accurate predictive models, expanding the clinical applicability of precision medicine in parotid tumors.

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