Journal of Environmental Biology
p-ISSN: 0254-8704 • e-ISSN: 2394-0379 • CODEN: JEBIDP

JEB®

Original Research Paper
Volume 47 Issue 4 July 2026 pp. 957-963
DOI: http://doi.org/10.22438/jeb/47/4(SI)/SPL-15

J. Environ. Biol., 2026

Journal website : www.jeb.co.in ★ E-mail : editor@jeb.co.in

Comprehensive analysis of genetic and epigenetic factors in oropharyngeal carcinoma: Integrating GWAS data with functional pathway analysis

G. Padmavathi[1]*, N. Uday Kumar[2], D. Dhanusha[2] and S. Vasishta[3]

[1]*Department of Anatomy, Apollo Institute of Medical Sciences and Research Chittoor - 517 127, India*
[2]*Department of General Surgery, Apollo Institute of Medical Sciences and Research Chittoor - 517 127, India*
[3]*Department of Biochemistry, Apollo Institute of Medical Sciences and Research Chittoor - 517 127, India*

Received: 29 November 2025 **Revised:** 04 May 2026 **Accepted:** 30 May 2026

***Corresponding Author Email:** drpadmavathi@aimsrchittoor.edu.in ***ORCiD:** https://orcid.org/0000-0003-1680-6386

Abstract

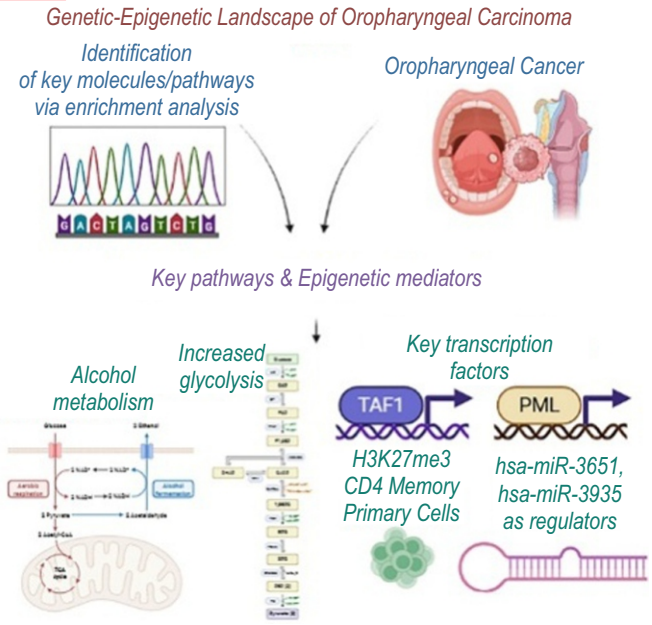
Aim: Oropharyngeal carcinoma (OPC) is a complex malignancy shaped by inherited susceptibility, environmental exposures, and regulatory mechanisms. Despite genome-wide association studies (GWAS) identifying multiple associated loci, their downstream biological relevance and interactions with metabolic and epigenetic factors remain inadequately characterised. This study systematically integrated GWAS-identified genes with functional bioinformatic analyses to elucidate molecular processes contributing to OPC.

Methodology: GWAS-implicated genes were subjected to pathway and process enrichment, transcription factor binding prediction, microRNA target enrichment, and cell-type–specific marker identification. Statistical evaluation employed p-values, adjusted p-values, odds ratios, and combined enrichment scores. Associated metabolites and histone modification signatures were examined to contextualise findings within broader regulatory frameworks.

Results: Enrichment analyses revealed strong overrepresentation of alcohol-related metabolic pathways, particularly ethanol oxidation (OR = 3331.00), and retinol/retinoic acid metabolism (OR = 1498.13). Significantly associated metabolites included ethanol, acetaldehyde, retinol, and retinal. MicroRNA enrichment implicated miR-3924 and miR-511-3p (OR > 50), whilst epigenetic profiling highlighted H3K27me3 and selected acetylation marks. Cell marker analysis indicated enrichment for LGR5-positive stem cells and basal epithelial cells.

Interpretation: These findings outline a multifactorial landscape in oropharyngeal carcinoma, wherein genetic susceptibility modulated through epigenetic and cell-type–specific regulatory contexts, offering candidate features for future experimental validation.

Key words: Alcohol metabolism, Epigenetic regulation, Genome-wide association study, Oropharyngeal carcinoma, Retinol metabolism



How to cite: Padmavathi, G., N. Uday Kumar, D. Dhanusha and S. Vasishta: Comprehensive analysis of genetic and epigenetic factors in oropharyngeal carcinoma: Integrating GWAS data with functional pathway analysis. *J. Environ. Biol.*, **47**, 957-963 (2026).

Introduction

Oropharyngeal carcinoma (OPC) constitutes a substantial component of the global cancer burden, with annual incidence estimates approaching half a million new cases worldwide (Lorenzoni *et al.,* 2022). Over recent decades, epidemiological patterns of OPC have shown noticeable shifts, particularly in economically developed regions, where incidence continues to rise even as traditional risk factors such as tobacco consumption demonstrate declining trends (Lechner *et al.,* 2022). This change has drawn attention to additional etiological contributors, among which infection with human papillomavirus (HPV) has emerged as a major determinant, complementing the long-recognized influences of alcohol intake and smoking (Shinomiya and Nibu, 2023). Despite these recognized exposures, inter-individual variation in OPC susceptibility suggests that inherited genetic factors also play a significant role. Genome-wide association studies have identified multiple single nucleotide polymorphisms associated with OPC risk; however, a substantial proportion of these variants lie within non-coding regions of the genome, complicating direct interpretation of their biological consequences (Chien *et al.,* 2023).

Moreover, OPC is unlikely to be driven by single-gene effects alone, instead reflecting cumulative and interacting influences of multiple loci alongside environmental factors, a situation that necessitates integrative analytical strategies (Miranda-Galvis *et al.,* 2021). Advances in functional genomics and epigenomic profiling provide opportunities to bridge the gap between statistical genetic associations and mechanistic understanding. Epigenetic features, particularly histone modifications such as trimethylation of histone H3 at lysine 27 (H3K27me3) and various acetylation marks, have been recognized as important regulators of chromatin structure and gene expression, with growing evidence implicating them in oncogenic processes (Beacon *et al.,* 2021). In parallel, microRNAs (miRNAs) have gained attention as post-transcriptional regulators capable of simultaneously modulating networks of genes within shared pathways, thereby exerting broad biological effects (Nunes *et al.,* 2025).

Alcohol consumption remains one of the strongest environmental risk factors for OPC, with risk increasing in a dose-dependent manner (Varghese and Dakhode, 2022). Biologically, ethanol metabolism generates acetaldehyde, a highly reactive compound capable of forming DNA adducts and promoting genomic instability (Lózsa *et al.,* 2026). Genetic variability within enzymes responsible for alcohol and aldehyde metabolism, including alcohol dehydrogenase and aldehyde dehydrogenase families, has been shown to influence cancer susceptibility across populations (Hibberd *et al.,* 2020). Retinoid signaling pathways represent another area of relevance in head and neck carcinogenesis. Retinoids are central to the regulation of epithelial cell differentiation, proliferation, and programmed cell death, and disruptions in retinoid metabolism or signaling have been documented in premalignant and malignant lesions of head and neck (Chen *et al.,* 2022; Cortés-Malagón *et al.,* 2024). Importantly, alcohol exposure can interfere with retinoid metabolism, potentially linking these two major risk factors at a biochemical level (Ferdouse and Clugston, 2024). The cellular origins of OPC are not fully resolved, with evidence supporting contributions from basal epithelial layers as well as specialized stem or progenitor cell populations (Gunduz *et al.,* 2021). Markers such as LGR5 have been detected in head and neck cancer stem-like cells, suggesting that genetic and epigenetic alterations within these compartments may be particularly relevant to tumor initiation and progression (Maharajan *et al.,* 2025).

In this context, integrating GWAS-derived genetic information with functional pathway, regulatory, and cellular analyses may provide a more complete picture of OPC pathogenesis. The present study, therefore, seeks to explore the molecular basis of OPC through a systematic examination of GWAS-implicated genes using multi-layered bioinformatics approaches. Specifically, the objectives include identifying key biological pathways and processes associated with OPC-linked variants, examining regulatory mechanisms such as miRNA targeting and transcription factor binding, evaluating the role of epigenetic histone marks, investigating potential cellular origins through marker enrichment, and incorporating metabolomic associations to contextualize genetic findings within metabolic networks relevant to disease development and progression.

Materials and Methods

Data collection and preprocessing: Genome-wide association study data relevant to oropharyngeal carcinoma were compiled from publicly accessible repositories, with particular reliance on the GWAS Catalog (Sollis *et al.,* 2023). Studies published between 2015 and 2024 were screened, and genes reported as significantly associated with OPC risk were extracted to generate a consolidated gene set for downstream analyses.

Functional and regulatory analyses: Functional enrichment analyses were conducted using the Enrichr platform, drawing upon pathway and ontology databases including KEGG (Sollis *et al.,* 2023), Reactome, and Gene Ontology categories encompassing Biological Process, Molecular Function, and Cellular Component. Enrichment significance was evaluated using Fisher's exact test, followed by Benjamini–Hochberg correction for multiple testing, with thresholds set at adjusted $p < 0.05$ and odds ratio > 1.5.Epigenetic regulation was explored through enrichment of histone modification marks derived from Epigenomics Roadmap datasets, focusing on H3K27me3, H3K4me3, H3K4me1 and histone acetylation signatures. Post-transcriptional regulation was assessed by microRNA target enrichment using miRTarBase (Cui *et al.,* 2024) and TargetScan (Min and Yoon, 2010), while transcription factor binding site enrichment was examined using ENCODE datasets and protein–protein interaction information. Metabolite associations linked to the GWAS gene set were also identified through Enrichr-based analyses.

Table 1: Epigenomics Roadmap HM ChIP-seq

Index	Name	p-value	Adjusted p-value	Odds Ratio	Combined score
1	H3K27me3 CD4 Memory Primary Cells	0.05273	0.9910	7.81	22.99
2	H3K23ac IMR90	0.05369	0.9910	6.22	18.19
3	H3K14ac IMR90	0.08161	0.9910	5.08	12.74
4	H4K5ac IMR90	0.08957	0.9910	5.92	14.28
5	H3K4me1 Duodenum Smooth Muscle	0.1111	0.9910	4.93	10.83

Table 2: TargetScan microRNA 2017

Index	Name	p-value	Adjusted p-value	Odds Ratio	Combined score
1	hsa-miR-3651	0.03042	0.4094	10.74	37.50
2	hsa-miR-3935	0.05666	0.4094	7.49	21.49
3	hsa-miR-3146	0.05954	0.4094	7.27	20.50

Statistical and visualization framework: All computational analyses were performed using R version 4.2.0 in conjunction with the Enrichr application programming interface. Data visualization and graphical summaries were generated using the ggplot2 package.

Results and Discussion

Analysis of histone modification enrichment patterns revealed several features of potential relevance to OPC-associated genes (Table 1). Enrichment of H3K27me3 marks was observed in CD4 memory primary cells (p = 0.05273, OR = 7.81), suggesting that repressive chromatin states may influence expression of genes linked to OPC susceptibility (Cai *et al.,* 2021). In addition, selected acetylation marks showed enrichment in IMR90 cells, including H3K23ac (p = 0.05369, OR = 6.22), H3K14ac (p = 0.08161, OR = 5.08), and H4K5ac (p = 0.08957, OR = 5.92). Although some values approach conventional significance thresholds, collectively they point towards a complex epigenetic regulatory landscape associated with OPC-related loci. The epigenetic findings carry meaningful biological implications when read alongside the OPC literature. The H3K27me3 mark is deposited primarily by the EZH2-containing PRC2 complex, which is known to be overexpressed or hyperactivated in various head and neck cancers (Xia *et al.,* 2022). Its enrichment, specifically, in CD4 memory primary cells raises an interesting possibility — that some of the GWAS-associated OPC genes may be subject to immune-cell-specific epigenetic silencing, potentially influencing the tumour immune microenvironment in OPC (Yang and Wang, 2021).

Conversely, the activating acetylation marks (H3K23ac, H3K14ac, H4K5ac) enriched in IMR90 fibroblast cells suggest a cell-type-dependent regulatory switch, where the same gene set can be in an active chromatin state in stromal cells while being repressed in immune compartments. This context-dependent epigenetic regulation may well contribute to the variable penetrance of genetic OPC risk across individuals with different tissue microenvironments — something that GWAS alone cannot easily capture but becomes visible through this kind of integrative epigenomic analysis (Friedman *et al.,* 2023).

MicroRNA target enrichment analyses identified multiple miRNAs with significant associations to the OPC gene set (Table 2). Notably, miRTarBase results highlighted hsa-miR-3924 (p = 0.001412, OR = 55.11), hsa-miR-511-3p (p = 0.001653, OR = 50.80), and hsa-miR-223-5p (p = 0.001953, OR = 46.60). The strength of these associations suggest that post-transcriptional regulation by specific miRNAs may contribute to coordinated modulation of OPC-relevant pathways. These miRNA findings deserve closer attention in terms of their mechanistic implications. hsa-miR-3924 and hsa-miR-511-3p are not yet extensively characterised in OPC specifically, but their very high odds ratios — exceeding 50 — indicate that these miRNAs are targeting a disproportionately large fraction of the GWAS-derived OPC gene set (Mazurek *et al.,* 2022). This is consistent with a scenario where a small number of post-transcriptional regulators simultaneously modulate entire clusters of susceptibility-related genes, rather than acting on isolated targets. hsa-miR-223-5p has a somewhat better-established profile in squamous cell carcinoma biology, where it has been linked to regulation of inflammatory responses and cell proliferation pathways. The TargetScan predictions for hsa-miR-3651, hsa-miR-3935, and hsa-miR-3146, though at lower odds ratios, further support the idea of multi-miRNA convergence on OPC-relevant gene networks. From a translational standpoint, these miRNA candidates represent viable targets for functional validation studies, given the growing interest in miRNA-based therapeutic approaches in head and neck cancer management.

Evaluation of transcription factor enrichment indicated potential regulatory involvement of TAF1 (p = 0.04203, OR = 29.15) and PML (p = 0.04372, OR = 27.99) (Table 3). These transcription factors may act as upstream regulators, influencing

Table 3: Transcription factor enrichment

Index	Name	p-value	Adjusted p-value	Odds Ratio	Combined score
1	TAF1	0.04203	0.04372	29.15	92.40
2	PML	0.04372	0.04372	27.99	87.61

Table 4: Reactome Pathways 2024

Index	Name	p-value	Adjusted p-value	Odds Ratio	Combined score
1	Ethanol oxidation	p<0.05	1.319e-8	3331.00	67363.52
2	Phase I - functionalization of compounds	p<0.05	0.000005581	292.54	3944.20
3	Biological oxidations	p<0.05	0.00003539	135.45	1521.10
4	RA biosynthesis pathway	p<0.05	0.01098	237.79	1237.70
5	Signaling by retinoic acid	p<0.05	0.01457	124.72	571.77

expression of multiple genes implicated through GWAS, thereby contributing to broader transcriptional programs relevant to OPC pathogenesis. Reactome pathway analysis demonstrated highly significant enrichment of metabolic pathways related to ethanol processing and oxidative metabolism (Table 4). Among these, ethanol oxidation ($p < 0.05$, OR = 3331.00), phase I functionalization of compounds ($p < 0.05$, OR = 292.54), and biological oxidations ($p < 0.05$, OR = 135.45) were particularly prominent. Pathways related to retinoic acid biosynthesis and signaling were also enriched, including the retinoic acid biosynthesis pathway ($p < 0.05$, OR = 237.79) and signaling by retinoic acid ($p < 0.05$, OR = 124.72).

The transcription factor enrichment results add an important upstream regulatory dimension to the overall picture. TAF1, the largest subunit of the TFIID basal transcription complex, plays a central role in RNA polymerase II-dependent transcription initiation at core promoters (Bernardini *et al.,* 2023). Its enrichment here suggests that disruption of basal transcriptional machinery itself — not merely individual regulatory genes — may be one mechanism through which OPC susceptibility loci influence broader gene expression programmes. PML is classically regarded as a tumour suppressor whose nuclear bodies serve as platforms for p53 stabilization, apoptosis regulation, and DNA damage response coordination (Liebl and Hofmann, 2022). Loss of PML expression has been documented in head and neck squamous cell carcinoma and correlates with poor tumour differentiation. The co-enrichment of both TAF1 and PML as upstream regulators of GWAS-implicated genes suggests a dual mechanism — aberrant transcription initiation working alongside compromised tumour suppressor activity — creating a permissive transcriptional environment for OPC-associated gene expression dysregulation.

KEGG pathway analysis further supported these findings (Table 5), with significant enrichment observed for tyrosine metabolism ($p < 0.05$, OR = 907.36), fatty acid degradation ($p < 0.05$, OR = 748.31), and pyruvate metabolism ($p < 0.05$, OR = 680.15). Pathways directly linked to alcohol and retinol metabolism, such as glycolysis/gluconeogenesis ($p < 0.05$, OR = 467.13) and retinol metabolism ($p < 0.05$, OR = 459.92), were also significantly represented. The Reactome enrichment data provides some of the most mechanistically compelling evidence in this entire analysis. The extraordinary odds ratio for ethanol oxidation (OR = 3331.00) reflects the deep concentration of alcohol metabolism genes within the OPC GWAS gene set — meaning that inherited variants associated with OPC risk are disproportionately located in and around genes responsible for ethanol breakdown and its toxic metabolite handling.

The enrichment of phase I functionalization pathways (OR = 292.54), which include cytochrome P450 enzymes, further situates the OPC gene set within broader xenobiotic metabolism biology that overlaps extensively with the ADH/ALDH alcohol axis (Esteves *et al.,* 2021). The simultaneous enrichment of retinoic acid biosynthesis (OR = 237.79) and retinoic acid signalling (OR = 124.72) pathways alongside ethanol oxidation is particularly meaningful, because it computationally recapitulates a well-known biochemical interaction: chronic alcohol exposure competes with retinol for the same NAD+-dependent ADH enzymes, thereby reducing retinoic acid synthesis and impairing normal epithelial differentiation in the oropharynx. Our findings are, therefore, consistent with a model where alcohol and retinoid metabolism are not simply co-occurring OPC risk factors, but are mechanistically linked through shared enzymatic machinery encoded by GWAS-implicated susceptibility genes.

Beyond pathway-level observations, integrative analysis across protein–protein interaction networks identified YKE2, DJP1 and SUMO1 as central nodes, suggesting their involvement as hubs within interconnected signaling or regulatory systems. Metabolite enrichment analysis revealed strong associations with alcohol- and catecholamine-related compounds, including 3,4-dihydroxyphenylglycol, chloral hydrate

Table 5: Summary of enrichment analysis results showing the term name, corresponding p-value, adjusted p-value (corrected for multiple testing), odds ratio indicating the strength of association, and the combined score representing the overall significance and enrichment magnitude

Index	Name	p-value	Adjusted p-value	Odds Ratio	Combined score
1	Tyrosine metabolism	p<0.05	p<0.05	907.36	15193.90
2	Fatty acid degradation	p<0.05	p<0.05	748.31	12121.48
3	Pyruvate metabolism	p<0.05	p<0.05	680.15	10831.83
4	Glycolysis / Gluconeogenesis	p<0.05	p<0.05	467.13	6934.07
5	Retinol metabolism	p<0.05	p<0.05	459.92	6806.34

and ethanol, reinforcing the prominence of dysregulated alcohol and retinoid metabolism (Leclercq *et al.,* 2024). Gene Ontology results were consistent with these patterns, with biological processes dominated by retinol, retinoic acid, and primary alcohol metabolism, while molecular function categories emphasized NAD^+-dependent dehydrogenase activities. Cellular component analysis pointed towards ciliary structures as additional elements of relevance. CellMarker dataset interrogation showed enrichment for LGR5-positive stem cells, basal epithelial cells, and progenitor populations across tissues, with markers also implicating hematopoietic, mesenchymal and epithelial stem cell compartments. RNA-seq GEO signature analysis indicated that the GWAS-derived gene set was enriched among downregulated genes in tissue differentiation and disease-related contexts, including mucosal and airway epithelia. Collectively, these layered observations suggest convergence of genetic susceptibility on metabolic pathways, regulatory networks, and specific cellular contexts relevant to OPC.

The KEGG pathway results complement and extend the Reactome findings in several important ways. The strong enrichment of tyrosine metabolism (OR = 907.36) connects the OPC gene set to catecholamine biosynthesis and degradation — a linkage that finds biological support in the metabolite enrichment data showing associations with 3,4-dihydroxyphenylglycol and related catecholamine compounds. Adrenergic signalling, which operates through catecholamine-dependent mechanisms, has been increasingly recognised as a modulator of tumour progression and immune evasion in head and neck cancers, lending credibility to this enrichment finding beyond mere statistical coincidence. Fatty acid degradation (OR = 748.31) and pyruvate metabolism (OR = 680.15) reflect the metabolic reprogramming that characterises many epithelial malignancies, where cancer cells shift between glycolytic and oxidative phosphorylation states depending on nutrient availability. The simultaneous enrichment of glycolysis/gluconeogenesis (OR = 467.13) and retinol metabolism (OR = 459.92) provides strong computational evidence for the biochemical interconnectedness of alcohol and vitamin A metabolism in OPC, as both pathways rely on NAD+-dependent dehydrogenase enzymes—exactly the molecular function category highlighted in our Gene Ontology analysis (Park *et al.,* 2024). In this study, GWAS-focused analysis of oropharyngeal carcinoma underscores the dominant involvement of alcohol-related metabolic pathways, with particularly strong enrichment for ethanol oxidation ($p < 0.05$, OR = 1664.75), in line with established epidemiological evidence linking alcohol consumption to OPC risk (Lee *et al.,* 2019; Rehm, 2011). The metabolic conversion of ethanol to acetaldehyde provides a plausible biological mechanism for carcinogenic effects. Retinoid metabolism and signaling pathways were similarly enriched, including the retinol metabolic process ($p < 0.05$, OR = 1498.13) and retinoic acid metabolic process ($p < 0.05$, OR = 1361.80) (Gudas, 2022), supporting the idea that alcohol-induced disruption of retinoid homeostasis may contribute to disease development. Epigenetic regulation emerged as an additional layer of relevance, with enrichment of repressive H3K27me3 marks alongside activating acetylation signatures such as H3K23ac, H3K14ac, and H4K5ac, pointing toward altered chromatin regulation in OPC-associated gene networks (Fanfarillo et al., 2024). The strong associations observed for miRNAs including hsa-miR-3924, hsa-miR-511-3p, and hsa-miR-223-5p are notable, particularly given previous links between miR-223 and head and neck cancers (Bhattacharjee *et al.,* 2023).

Cell-type enrichment for LGR5-positive stem cells and basal epithelial markers suggests potential relevance to tumor-initiating populations (Lee *et al.,* 2025). Transcription factors TAF1 and PML may function as higher-level regulators coordinating these processes. Viewing all these layers of evidence together, a coherent and biologically plausible model of OPC susceptibility emerges from this study. At the genetic level, GWAS-derived variants cluster around genes encoding enzymes of alcohol and retinoid metabolism — primarily the ADH/ALDH family. At the pathway level, these genes are embedded in tightly enriched networks spanning ethanol oxidation, retinoic acid signalling, and broader oxidative and energy metabolism. At the regulatory level, the gene set appears modulated by specific miRNAs — notably hsa-miR-3924, hsa-miR-511-3p, and the miR-223 family — as well as by transcription factors TAF1 and PML operating at a higher level of transcriptional control. Epigenetically, context-dependent chromatin states are evident: repressive H3K27me3 marks in immune cell compartments alongside activating acetylation marks in stromal cell contexts.

At the cellular level, enrichment for LGR5-positive stem cells and basal epithelial markers suggests that these genetic and epigenetic alterations are particularly relevant within tumour-

initiating populations of the oropharyngeal epithelium. What is perhaps most striking about these findings is their internal consistency across independent analytical platforms—the metabolomic, epigenomic, transcriptomic, pathway, and cell-type data all point in the same biological direction. This convergent evidence across multiple analytical layers lends credibility to the computational model and highlights the value of integrative bioinformatics as a hypothesis-generating framework for multifactorial diseases like OPC. Future studies should prioritise functional validation of ADH/ALDH pathway genes in oropharyngeal epithelial cell lines, experimental manipulation of the identified miRNAs to confirm their regulatory roles over OPC susceptibility genes, and chromatin immunoprecipitation assays to validate H3K27me3 enrichment at specific OPC risk loci.

It should be emphasized that the present investigation is entirely based on computational and bioinformatics analyses without experimental or clinical validation. Additionally, dataset normalization was not performed, which could influence the precision of enrichment outcomes. As such, the findings should be interpreted cautiously and regarded as exploratory. Further *in-vitro, in-vivo,* and functional studies will be essential to substantiate and refine the biological significance of the pathways, regulators and cellular contexts identified here.

Acknowledgment

Authors thank the Central Research Laboratory for Molecular Genetics, Bioinformatics and Machine Learning at Apollo Institute of Medical Sciences and Research Chittoor Murukambattu-517127, Andhra Pradesh, India for the infrastructure.

Authors' contribution: G. Padmavathi, N. Uday Kumar, D. Dhanusha and S. Vasishta: All contributed equally to the study's design, data acquisition, analysis, and manuscript preparation.

Funding: Not applicable.

Research content: The research content of manuscript is original and has not been published elsewhere.

Ethical approval: Not applicable.

Conflict of interest: The authors declare that there is no conflict of interest.

Data availability: Not applicable.

Consent to publish: All authors agree to publish the paper in *Journal of Environmental Biology.*

References

Beacon, T.H., G.P. Delcuve, C. López, G. Nardocci, I. Kovalchuk, A.J. van Wijnen and J.R. Davie: The dynamic broad epigenetic (H3K4me3, H3K27ac) domain as a mark of essential genes. *Clin. Epigenetics,* **13**, 138 (2021).

Bernardini, A., P. Mukherjee, E. Scheer, I. Kamenova, S. Antonova, P.K. Mendoza Sanchez, G. Yayli, B. Morlet, H.T.M. Timmers and L. Tora: Hierarchical TAF1-dependent co-translational assembly of the basal transcription factor TFIID. *Nat. Struct. Mol. Biol.,* **30**, 1141-1152 (2023).

Bhattacharjee, B., A.F. Syeda, D. Rynjah, S.M. Hussain, S.C. Bora, P. Pegu, R.K. Sahu and J. Khan: Pharmacological impact of microRNAs in head and neck squamous cell carcinoma: Prevailing insights on molecular pathways, diagnosis, and nanomedicine treatment. *Front. Pharmacol.,* **14**, 1174330 (2023).

Cai, Y., Y. Zhang, Y.P. Loh, J.Q. Tng, M.C. Lim, Z. Cao, A. Raju, E.L. Aiden, S. Li, L. Manikandan, V. Tergaonkar, G. Tucker-Kellogg and M.J. Fullwood: H3K27me3-rich genomic regions can function as silencers to repress gene expression via chromatin interactions. *Nat. Commun.,* **12**, 719 (2021).

Chen, S., Q. Hu, X. Tao, J. Xia, T. Wu, B. Cheng and J. Wang: Retinoids in cancer chemoprevention and therapy: Meta-analysis of randomized controlled trials. *Front. Genet.,* **13**, 1065320 (2022).

Chien, H.T., C.L. Tsai, C.K. Young, Y.S. Lee, C.T. Liao, C.C. Yeh, A. Chao, K.L. Cho, C.H. Chen and S.F. Huang: Single-nucleotide polymorphism at alcohol dehydrogenase 1B: A susceptible gene marker in oro-/hypopharyngeal cancers from genome-wide association study. *Cancer Med.,* **12**, 19174-19187 (2023).

Cortés-Malagón, E.M., P. Gariglio, M. Sierra-Martínez and J. Bonilla-Delgado: Retinoids: Molecular aspects and treatment in premalignant lesions and cervical cancer. *Cancer Control,* **31**, 10732748241279514 (2024).

Cui, S., S. Yu, H.Y. Huang, Y.C.D. Lin, Y. Huang, B. Zhang, J. Xiao, H. Zuo, J. Wang, Z. Li, G. Li, J. Ma, B. Chen, H. Zhang, J. Fu, L. Wang and H.D. Huang: MiRTarBase 2025: Updates to the collection of experimentally validated microRNA-target interactions. *Nucl. Acids Res.,* **53**, D147-D156 (2024).

Esteves, F., J. Rueff and M. Kranendonk: The central role of cytochrome P450 in xenobiotic metabolism-a brief review on a fascinating enzyme family. *J. Xenobiot.,* **11**, 94-114 (2021).

Fanfarillo, F., G. Ferraguti, M. Lucarelli, A. Fuso, M. Ceccanti, S. Terracina, G. Micangeli, L. Tarani and M. Fiore: The impact of alcohol-induced epigenetic modifications in the treatment of alcohol use disorders. *Curr. Med. Chem.,* **31**, 5837-5855 (2024).

Ferdouse, A. and R.D. Clugston: Modest effect of differential dietary vitamin A intake on the pathogenesis of alcohol-associated liver disease. *Alco. Clin. Exp. Res.,* **48**, 1036-1049 (2024).

Friedman, M.J., H. Lee, J.Y. Lee and S. Oh: Transcriptional and epigenetic regulation of context-dependent plasticity in T-helper lineages. *Imm. Netw.,* **23**, e5 (2023).

Gudas, L.J.: Retinoid metabolism: New insights. *J. Mol. Endocrinol.*, **69**, T37-T49 (2022).

Gunduz, M., E. Gunduz, S. Tamagawa, K. Enomoto and M. Hotomi: Cancer stem cells in oropharyngeal cancer. *Cancers,* **13**, 3878 (2021).

Hibberd, R., E. Golovina, S. Farrow and J.M. O'Sullivan: Genetic variants associated with alcohol dependence co-ordinate regulation of ADH genes in gastrointestinal and adipose tissues. *Sci. Rep.,* **10**, 9897 (2020).

Lechner, M., J. Liu, L. Masterson and T.R. Fenton: HPV-associated oropharyngeal cancer: Epidemiology, molecular biology and clinical management. *Nat. Rev. Clin. Oncol.,* **19**, 306-327 (2022).

Leclercq, S., H. Ahmed, C. Amadieu, G. Petit, V. Koistinen, Q. Leyrolle, M. Poncin, P. Stärkel, E. Kok, P.J. Karhunen, P. de Timary, S. Laye, A.M. Neyrinck, O.K. Kärkkäinen, K. Hanhineva and N. Delzenne: Blood metabolomic profiling reveals new targets in the management of psychological symptoms associated with severe

alcohol use disorder. *Elife,* **13**, 96937 (2024).
Lee, H., B. Kim, J. Park, S. Park, G. Yoo, S. Yum, W. Kang, J.M. Lee, H. Youn and B. Youn: Cancer stem cells: Landscape, challenges and emerging therapeutic innovations. *Signal Transduct. Target. Ther.,* **10**, 248 (2025).
Lee, Y.J., M.G. Yoo, H.K. Kim, H.B. Jang, K.J. Park, H.J. Lee, S.G. Kim and S.I. Park: The association between alcohol metabolism and genetic variants of ADH1A, SRPRB and PGM1 in Korea. *Alcohol,* **79**, 137-145 (2019).
Liebl, M.C. and T.G. Hofmann: Regulating the p53 tumor suppressor network at PML biomolecular condensates. *Cancers,* **14**, 4549 (2022).
Lorenzoni, V., A.K. Chaturvedi, J. Vignat, M. Laversanne, F. Bray and S. Vaccarella: The current burden of oropharyngeal cancer: A global assessment based on GLOBOCAN 2020. *Cancer Epidemiol. Biomarkers Prev.,* **31**, 2054-2062 (2022).
Lózsa, R., B. Szikriszt, E. Németh, Z. Szeltner, R. Martinek, Á. Póti, T. Feik, S. Kollarics, B.G. Márkus, N. Kanu, Z. Sztupinszki, F. Simon, T. Shibata, C. Swanton, Z. Szallasi, A.L. Richardson and D. Szüts: Long-term exposure to the ethanol-derived metabolite acetaldehyde elevates structural genomic alterations but not base substitutions. *Commun. Biol.,* **9**, 243 (2026).
Maharajan, N., D.S. Benyamien-Roufaeil, R.A. Brown, B.A. Portney, A. Banerjee and M. Zalzman: Cancer stem cell mechanisms and targeted therapeutic strategies in head and neck squamous cell carcinoma. *Cancer Lett.,* **634**, 218015 (2025).
Mazurek, M., R. Mlak, I. Homa-Mlak, T. Powrózek, A. Brzozowska, W. Kwaśniewski, G. Opielak and T. Małecka-Massalska: High miR-511-3p expression as a potential predictor of a poor nutritional status in head and neck cancer patients subjected to intensity-modulated radiation therapy. *J. Clin. Med.,* **11**, 805 (2022).
Min, H. and S. Yoon: Got target? Computational methods for microRNA target prediction and their extension. *Exp. Mol. Med.,* **42**, 233-244 (2010).
Miranda-Galvis, M., R. Loveless, L.P. Kowalski and Y. Teng: Impacts of environmental factors on head and neck cancer pathogenesis and progression. *Cells,* **10**, 389 (2021).
Nunes, S., R. Bastos, A.I. Marinho, R. Vieira, I. Benício, M.A. de Noronha, S. Lírio, C. Brodskyn and N.M. Tavares: Recent advances in the development and clinical application of miRNAs in infectious diseases. *Non-Coding RNA Res.,* **10**, 41-54 (2025).
Park, S., P. Jebamani, Y.G. Seo and S. Wu: Computational study of network and type-I functional divergence in alcohol dehydrogenase enzymes across species using molecular dynamics simulation. *Biomolecules,* **14**, 1473 (2024).
Rehm, J.: The risks associated with alcohol use and alcoholism. *Alcohol Res. Hlth.,* **34**, 135-143 (2011).
Shinomiya, H. and K.I. Nibu: Etiology, diagnosis, treatment, and prevention of human papilloma virus-associated oropharyngeal squamous cell carcinoma. *Int. J. Clin. Oncol.,* **28**, 975-981 (2023).
Sollis, E., A. Mosaku, A. Abid, A. Buniello, M. Cerezo, L. Gil, T. Groza, O. Güneş, P. Hall, J. Hayhurst, A. Ibrahim, Y. Ji, S. John, E. Lewis, J.A.L. MacArthur, A. McMahon, D. Osumi-Sutherland, K. Panoutsopoulou, Z. Pendlington, S. Ramachandran, R. Stefancsik, J. Stewart, P. Whetzel, R. Wilson, L. Hindorff, F. Cunningham, S.A. Lambert, M. Inouye, H. Parkinson and L.W. Harris: The NHGRI-EBI GWAS catalog: Knowledgebase and deposition resource. *Nucl. Acids Res.,* **51**, D977-D985 (2023).
Varghese, J. and S. Dakhode: Effects of alcohol consumption on various systems of the human body: A systematic review. *Cureus,* **14**, e30057 (2022).
Xia, J., J. Li, L. Tian, X. Ren, C. Liu and C. Liang: Targeting enhancer of zeste homolog 2 for the treatment of hematological malignancies and solid tumors: Candidate structure-activity relationships insights and evolution prospects. *J. Med. Chem.,* **65**, 7016-7043 (2022).
Yang, Y. and Y. Wang: Role of epigenetic regulation in plasticity of tumor immune microenvironment. *Front. Immunol.,* **12**, 640369 (2021).