Discover Oncology

Review

HOX gene dysregulation in glioblastoma: a narrative review of current advances

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Abstract
HOX (homeobox) genes are virtually absent in healthy adult brains but are detected in malignant brain tumors, particularly gliomas. In 2021, the World Health Organization (WHO) classified adult-type diffuse gliomas into three distinct categories: astrocytomas (isocitrate dehydrogenase [*IDH*]-mutated), oligodendrogliomas (*IDH*-mutated and 1p/19q-deleted), and glioblastomas, *IDH*-wildtype (GBM). GBM is the most common and aggressive primary malignant tumor of the Central Nervous System (CNS), characterized by its high recurrence rate and rapid growth. Dysregulation of *HOX* genes is a well-established phenomenon in both solid and liquid malignancies, playing crucial roles in various fundamental characteristics of cancer, including GBM. In recent years, *HOX* genes have gained recognition not only as key regulators of tumor progression but also as potential biomarkers for predicting disease outcomes and as promising therapeutic targets for GBM. This review compiles the latest research on *HOX* genes in GBM, encompassing studies published before and after the 2021 WHO classification of CNS tumors. Our goal is to provide a comprehensive overview of key findings on the role of *HOX* gene clusters, which are groups of genes involved in regulating the development of the body plan along the anterior–posterior axis, in GBM initiation, progression, prognosis, and treatment response.

Keywords Glioblastoma · *HOX* gene · Dysregulation/deregulation · Prognosis · Epigenetics · Temozolomide

1 Introduction

Glioblastoma (GBM) is the most common and lethal primary brain tumor in adults, with a median survival time of only about 14.6 months [46]. Despite the use of surgical resection, radiation therapy, and pharmaceutical interventions, only 9.8% of affected individuals survive beyond five years [5]. While GBM may be considered rare, its occurrence rate is estimated at roughly 10 per 100,000 individuals, posing a significant public health concern due to its poor prognosis [47]. The highest manifestation likelihood of GBM is observed within the 50 to 60 years age range [37, 42]. GBM was classified in the 2016 CNS4 World Health Organization (WHO) classification into three categories: (1) GBM, *IDH*-WT, which comprises

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approximately 90% of cases, (2) GBM, *IDH*-mutant, accounting for about 10% of cases, and (3) GBM, NOS (Not otherwise specified), used for tumors where complete *IDH* evaluation is not feasible [32].

However, the Consortium to Inform Molecular and Practical Approaches to Central Nervous System (CNS) Tumor Taxonomy (cIMPACT-NOW) update 3 proposed diagnostic criteria for diffuse gliomas with histologic grades 2 and 3, where *IDH*-wild type (*IDH*-wt) gliomas exhibiting epidermal growth factor receptor (*EGFR*) amplification, whole chromosome 7 gain and whole chromosome 10 loss (7 + /10 –), and *TERT* promoter (*pTERT*) mutations were recommended to be classified as GBM [4]. These gliomas were ultimately classified as GBM (WHO Grade 4) in the 2021 WHO Classification of CNS Tumors [32], which places greater emphasis on molecular markers compared to previous editions. The current composition of GBMs significantly differs from earlier counterparts due to the exclusion of all IDH-mutant astrocytoma's. Moreover, a substantial number of WHO grade 2–3 *IDH*-WT gliomas with distinct molecular characteristics were classified as GBM in the 2021 WHO CNS5 classification [32]. In addition to *ID*H mutation, *EGFR* amplification, *TERT* promoter mutation, and + 7/-10 chromosome copy-number variations, identifying other molecular alterations linked to GBM prognosis is crucial. These changes can help identify distinct subgroups for a more personalized treatment approach [2].

The *HOX* (homeobox) gene family is crucial for cell differentiation and vertebrate development. Over the past several decades, the aberrant expression of *HOX* genes in various tumors has captured the attention of researchers. Recent studies have illuminated the critical roles of specific *HOX* genes in tumor progression and their impact on clinical outcomes [6]. Scientific literature indicates that *HOX* gene expression can either increase or decrease in different tumors [6]. In GBM patients, altered *HOX* gene expression is associated with poor survival rates and predicts resistance to temozolomide (TMZ) therapy [36].

In humans, the 39 *HOX* genes are organized into four clusters, *HOXA*, *HOXB*, *HOXC*, and *HOXD*, located on chromosomes 7, 17, 12, and 2, respectively, as illustrated in Fig. 1 [33]. These genes encode regulatory transcription factors that are essential for embryonic development and are frequently dysregulated in cancer, where they influence cell fate determination and key cellular processes such as apoptosis and angiogenesis [60]. Initially, the *HOX* gene family was primarily studied for its role in axial patterning and body plan formation during embryogenesis [6], but increasing evidence has highlighted its involvement in tumor progression and therapeutic resistance.

HOXA genes are notably mutated and overexpressed in various cancers, including GBM, as demonstrated by analyses of CGGA (Chinese Glioma Genome Atlas) and TCGA ((The Cancer Genome Atlas) datasets. The diagnostic significance of the *HOXA* family is well-established, with *HOXA*-based nomogram models proving effective in predicting survival outcomes for GBM patients [62]. Additionally, several members of the *HOXB* cluster have been found to be dysregulated in glioma tissues, contributing to tumorigenesis [12]. The *HOXC* family is similarly upregulated across multiple solid tumor types, highlighting its broad role in cancer progression [3]. Furthermore, transcription factors within the *HOXD* cluster regulate key oncogenic processes, including tumor proliferation, migration, and invasion, making them promising candidates for both diagnostic and therapeutic targeting [48]. These findings highlight that

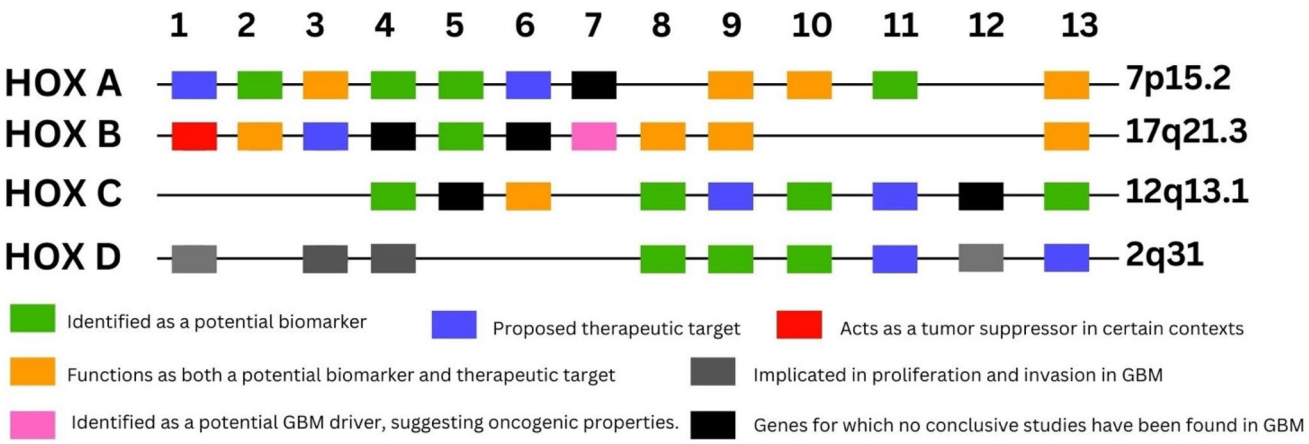

Fig. 1 The involvement of HOX genes in the hallmarks of GBM and their genomic organization across the four loci of *HOX* genes (*HOXA, HOXB, HOXC* and *HOXD*) with corresponding chromosomal locations on the right. The hallmarks of cancer include the clinical relevance of HOX genes, including their roles as potential biomarkers, proposed therapeutic targets, potential GBM drivers, regulators of proliferation and invasion, tumor suppressors in specific contexts, and genes for which no conclusive studies have been reported in GBM. Note: p represents the short arm of the chromosome, and q represents the long arm of the chromosome.

aberrant regulation across all four *HOX* gene clusters plays an important role in glioblastoma pathogenesis, which offer significant potential for the development of novel diagnostic biomarkers and targeted therapeutic strategies.

This review examines the role of *HOX* gene dysregulation in GBM progression, therapeutic resistance, and prognosis. By summarizing recent research, we provide a comprehensive overview of *HOX* gene involvement in tumor initiation, progression, and therapy response. A deeper understanding of these mechanisms could lead to improved prognostic markers and targeted therapies, aligning with the 2021 WHO classification and advancements in neuro-oncology.

2 Literature search approach

To gather information for this review article, we conducted a comprehensive search of publications on PubMed using keywords such as "*HOX* genes in GBM," "*HOXAs* in GBM," "*HOXBs* in GBM," "*HOXC*s in GBM," "*HOXDs* in GBM," "*HOX* gene signatures in GBM," "*HOX* gene and drug resistance in GBM," and "DNA methylation in GBM." Additionally, we searched for each of the 39 *HOX* gene cluster names individually to locate specific publications related to each *HOX* gene cluster in GBM. We also used Google Scholar with similar keywords to ensure a thorough search.

3 Summary of current research on HOX genes in GBM

To highlight the progress and significance of *HOX* gene cluster research in GBM, we compiled Table 1, which consolidates 48 studies investigating *HOX* gene expression in GBM. This table provides a structured summary of key studies, outlining the study design, examined *HOX* genes, and major findings related to GBM biology and patient outcomes. By organizing the information in this manner, we aim to offer readers a clear and accessible snapshot of which *HOX* genes have been most extensively studied, the experimental approaches used, and their potential impact on glioma prognosis and therapy. Notably, our review identified research covering the majority of *HOX* genes in GBM, with the exceptions of *HOXA7, HOXB4, HOXB6, HOXC5, and HOXC12*, where no studies were found. This comprehensive compilation not only enhances clarity but also directs readers toward emerging trends and potential gaps in the field, helping to guide future research efforts.

To provide a concise and comprehensive overview of *HOX* gene alterations in gliomas, we have created Supplementary Table 1, which aids in interpreting their roles in glioma progression and neuropathology. This table summarizing key *HOX* genes reported in association with astrocytoma (*IDH*-mutant), oligodendroglioma (*IDH*-mutant & 1p/19q codeleted), and glioblastoma (GBM, *IDH*-wildtype). Where relevant, we indicate whether studies have found these genes overexpressed, downregulated, or epigenetically modified in each subtype, along with key references.

4 Detailed insights into *HOX* gene clusters in GBM

The role of *HOX* genes in GBM has garnered significant attention due to their critical involvement in tumorigenesis, tumor progression, and therapeutic resistance. These genes, which are evolutionarily conserved transcription factors, are organized into four distinct family clusters: *HOXA*, *HOXB*, *HOXC*, and *HOXD*. Dysregulation of *HOX* gene expression, including overexpression, downregulation, and epigenetic modifications, has been widely observed in GBM, with profound implications for the prognosis and treatment response of patients. Although several studies have focused on the individual contributions of these genes, the complexity of their interactions within each family cluster remains a key area of ongoing research. This section will explore the findings related to each *HOX* family cluster, drawing on insights from current literature to highlight the diverse roles these genes play in the biology of GBM. While dysregulation is observed across all *HOX* gene clusters in GBM, evidence indicate that the *HOXA* cluster may exhibit a more pronounced alteration, highlighting higher expression levels and a stronger correlation with tumor progression and prognosis. This distinction demonstrates the importance of the unique regulatory mechanisms and therapeutic vulnerabilities associated with the *HOXA* cluster in contrast to the *HOXB*, *HOXC*, and *HOXD* clusters.

Table 1 Collection of the most recent publications that studied *HOX* genes in GBM patients

HOX Genes	Study Design/Method	Key Findings	Clinical Relevance	Reference
HOXA9-10, *HOXC4*, *HOXD9*	In silico (TCGA, GEO: GSE4536, GSE4290); used statistical methods	*HOX* genes are overexpressed in GBM tissues and stem cells, correlating with poor survival	Identifies potential combined *HOX-PBX* targets in GBM therapy. Potential biomarker for prognosis and therapeutic target	[1]
HOX genes (general)	Review covering *HOX* family in multiple cancers	Summarizes how *HOX* dysregulation contributes to hallmarks of cancer	Does not discuss the clinical implications and therapeutic potential of targeting *HOX* genes	[6]
All four *HOX* clusters	In silico (GEO: GSE161175, GSE161438, GSE161437, GSE161436, GSE161275); Epigenetic analyses	Identified widespread *HOX* overexpression in IDH-wt GBM linked to H3K27me3 depletion and alternative promoter usage	*HOX* gene upregulation via H3K27me3 loss offers biomarker and therapeutic potential for IDHwt glioma	[24]
HOXA5	In silico (TCGA, Fred Hutchinson CRC); In vivo PDGF-driven mouse GBM model	*HOXA5* linked to chromosome 7 gain and aggressive phenotype; overexpression correlates with radiation resistance	Potential driver of GBM progression and therapy resistance, new prognostic biomarker	[7]
HOXA9	In silico (UCSF, GEO: GSE4271, ONCOMINE, Connectivity Map) + in vitro	*HOXA9* overexpression confers poor survival in GBM; reversed via PI3K inhibition	*HOXA9* is a negative prognostic marker and possible epigenetic target for therapy	[8]
HOX genes (various)	In silico (GEO: GSE123678, GSE123682, GSE123892, GSE33587); Epigenetic analyses	Transcriptional alterations in GBM occur independently of DNA methylation; *HOX* genes dysregulated in *IDH*-wt tumors	H3K27me3 alterations and bivalent chromatin gene dysregulation offer targets for glioma epigenetic therapy	[9]
HOXD-AS2, *HOXD* genes	In silico (TCGA, GEO: GSE25632, Hi-C); Analysis of lncRNA expression	Promoter-enhancer RNAs regulate *HOXD3*, *HOXD4*/miR-10b activation; miR-10b as downstream in GBM	Potential *HOXD*-lncRNA-miR-10b regulatory axis for therapeutic targeting	[10]
HOXA13	In silico (CGGA, REMBRANDT, GEO: GSE16011, GSE4290) + in vitro	*HOXA13* promotes glioma proliferation/invasion via Wnt/β-catenin, TGF-β; upregulation correlates with higher grade and poor prognosis	Potential biomarker and therapeutic target for high-grade glioma	[11]
HOXB9	In vitro (First Hospital of Dalian Med. Univ.) + RT-PCR, WB, IHC	*HOXB9* overexpressed in higher-grade gliomas, suggesting role in progression	Potential new target or prognostic factor for glioma progression	[12]
HOXA10	In silico (TCGA) + GSC cultures + Western blots, immunohistochemistry,	Tumorigenic MLL-homeobox network in GBM stem cells; *HOXA10* as part of oncogenic network	The MLL-Homeobox network, including *HOXA10*, may aid glioblastoma stratification and treatment	[13]
HOXA9, HOXA10	In silico (TCGA, GEO: GSE19578); Pediatric GBM cells	MGMT-independent TMZ resistance linked to *HOX*/stem cell gene signature, including *HOXA9/HOXA10*	Reveals *HOX* gene involvement in chemoresistance, potential therapeutic targets	[14]
HOX genes	Review on *HOX* gene pathophysiology in various cancers	Summarizes *HOX* roles in hematopoiesis and cancer progression	Foundational background on *HOX* gene oncogenic mechanisms	[16]
HOXA6, HOXB13	In vitro (Glioma cell lines, First Hospital of Jilin Univ.)	Overexpression of these HOX genes correlated with invasive glioma behavior	Suggests *HOXA6*, *HOXB13* as potential therapeutic targets for invasive glioma	[18]
HOXC10	In silico (TCGA, ONCOMINE) + in vitro knockdown	*HOXC10* overexpression promotes GBM proliferation, migration, invasion via PI3K/AKT	Possible prognostic marker; inhibiting *HOXC10* might disrupt GBM growth	[17]
HOXA9	In silico (TCGA, GlioVis, GEO: GSE48865, GSE59612) + in vitro (U87MG)	*HOXA9* transcriptionally activates WNT6, fueling WNT/β-catenin pathway and poor prognosis	*HOXA9*–WNT6 axis is a potential GBM therapeutic target	[15]
HOXB1	In silico (CGGA, GEO: GSE4290) + qRT-PCR, IHC	Downregulation of *HOXB1* in high-grade gliomas suggests tumor-suppressive role	Downregulation of *HOXB1* expression correlates with more aggressive, higher-grade gliomas and poorer patient survival	[19]

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Table 1 (continued)

HOX Genes	Study Design/Method	Key Findings	Clinical Relevance	Reference
HOXA10	In silico (NCH_EORTC, TCGA); DNA methylation profiling	Hypermethylation of *HOXA* locus on chr7p15.2 co-occurs with HOX-high expression in GBM	*HOX*-gene-driven stem-cell signatures in glioblastoma, associated with treatment resistance, result from *HOXA* gene amplification on chromosome 7 and DNA hypermethylation	[23]
HOXA10	In vitro (Glioma cell lines LN18, LN229)	*HOXA10* involved in homologous recombination repair; linked to TMZ resistance	Therapeutic target for chemosensitization	[21]
HOXD1	In silico (TCGA), morphological analysis of GBM pathology	*HOXD1* among oligodendrocyte-related genes correlating with oligodendroglioma components in GBM	*HOXD1* expression may reflect oligodendroglial differentiation in GBM	[22]
HOXA1	In vitro (GBM cell lines) + RT-qPCR, RNA-FISH, ChIP (First Hospital of Jilin Univ.)	*HOXA1* overexpression via lncRNA-HOTAIRM1 boosts GBM proliferation, invasion	HOTAIRM1/*HOXA1* axis could be a promising therapeutic target for treating GBM	[27]
HOXD10	In silico (TCGA, CGGA, GEO: GSE74187, GSE4412)	*HOXD10* protein downregulated in GBM; role in cytokine-cytokine receptor interactions	Possible biomarker: mechanism requires further clarification	[29]
HOXC6	In silico (TCGA, GEO: GSE16011) + functional assays	*HOXC6* as an independent prognostic factor for GBM; linked to cell cycle regulation	Potential therapeutic target, could guide patient stratification	[30]
HOXA2	In silico (TCGA, CGGA)	*HOXA2* elevated in GBM correlates with poor prognosis	Identifies *HOXA2* as a possible GBM biomarker	[31]
HOX genes (general)	Review on *HOX* code, epigenetic considerations	Examines *HOX* gene functions in development and cancer	Possible basis for *HOX*-targeted therapies in GBM	[33]
HOXB2	In silico (ONCOMINE)	*HOXB2* overexpression in GBM correlates with poor prognosis	*HOXB2* is a potential biomarker and therapeutic target linked to poor GBM survival	[26]
HOXB8	In silico (EBI, CGGA, GEO); IHC, qPCR	*HOXB8* promotes glioma cell growth, migration, and invasion, possibly via *SAMD9* regulation and PI3K/AKT pathway activation	*HOXB8* is a potential biomarker and therapeutic target for glioblastoma, linked to aggressive tumors and poor survival	[34]
HOX genes (various)	In silico (GEO: GSE7696); microarray in GBM	*HOX*-dominated stem cell-like signature correlates with chemo-radiotherapy resistance	Early link between *HOX*/stem cell signature and poor GBM outcomes	[36]
HOXA3	In silico (TCGA)	*HOXA3* identified as TF in GBM via expression analyses	Potential biomarker or therapeutic target in GBM	[41]
HOXA9	In silico (TCGA, REMBRANDT)	*HOXA9* as prognostic factor; correlated with shorter survival in GBM	Important for GBM prognostic stratification	[40]
HOXA1-2, HOXB3, HOXC6/10/11, HOXD9/11,	In silico (ENA: ERP125425, GEO: GSE206357); chromatin & TF-binding studies	Multiple *HOX* TFs significantly expressed in GBM, controlling glioma progression via regulatory networks	Identifies a cluster of *HOX*-driven transcription factors as potential GBM drivers	[43]
HOXD8, HOXD13, HOXC4	In silico (TCGA, Birmingham) + DNA methylation analyses	Hypermethylation differences in GBM survivors, including *HOXD8, HOXD13, HOXC4*	*HOX* methylation might be a prognostic biomarker in GBM	[45]
HOXA11	In vitro microarray (initial vs. recurrent GBM pairs) + qRT-PCR	Underexpression of *HOXA11* linked to shorter survival, therapy resistance	*HOXA11* could serve as a predictive biomarker for GBM treatment response	[44]
HOXD1/3/4 HOXD8-13	Review referencing multiple in silico datasets	Emphasizes *HOX* transcription factors in various cancer hallmarks, including GBM	*HOX* genes play a key role in promoting proliferation, migration, invasion, and angiogenesis in GBM	[48]

Table 1 (continued)

HOX Genes	Study Design/Method	Key Findings	Clinical Relevance	Reference
HOXB13	In silico (TCGA) + patient samples (Jiangsu Province Hospital)	*HOXB13* overexpression correlated with poor GBM prognosis; lncRNA *HOXC-AS3* link	*HOXB13* promotes GBM progression via *HOXC-AS3*, making it a potential prognostic marker and therapeutic target	[50]
HOXC11	In silico (TCGA)	Identified *HOXC11* as a risk factor for GBM; included in 5-gene survival risk signature	May help prognostic modeling for GBM patients	[51]
HOXC9	In silico (R2 platform) + in vitro (Third Military Med. Univ.)	*HOXC9* drives GBM proliferation, blocks autophagy by inhibiting DAPK1/Beclin1	Potential therapeutic target modulating tumor growth and autophagy	[56]
HOXB5	In silico (TCGA, GTEx, CGGA) + expression analysis	HOX*B5* highly expressed in GBM, correlates with poor prognosis	Possible prognostic biomarker in GBM	[53]
HOXB3	In vitro (lentiviral-mediated RNA interference (RNAi)) + western blot analysis,	*HOXB3* upregulated in GBM cells, enhances proliferation and invasion	*HOXB3* may serve as a potential therapeutic target for GBM due to its role in promoting GBM cell proliferation and invasion	[55]
HOXD9	In silico (TCGA); hypoxic conditions in vitro	*HOXD9* enhances glycolysis and *HMGB1* secretion under hypoxia, driving tumor growth	HOXD9 is a potential prognostic biomarker and therapeutic target for GBM	[54]
HOXA3	In silico (TCGA, R2), in vitro validations	*HOXA3* and *KDM6A* drive aerobic glycolysis and GBM progression	Epigenetic mechanism linking *HOXA3*, *KDM6A*; potential therapy target	[58]
HOXC6	In silico (ONCOMINE, OncoLnc)	High *HOXC6* expression correlates with poor GBM prognosis, upregulates MAPK signaling	*HOXC6* promotes GBM progression via MAPK signaling, suggesting its potential as a biomarker and target	[57]
HOXC6, *C8*, *C10*, and *C13*	In silico (TCGA, GTEx, Oncomine)	All overexpressed in GBM; roles in immune infiltration and negative survival outcomes	Potential biomarkers for immune-based therapies or risk stratification	[59]
HOXA, HOXB, HOXC, HOXD	Database references (PhosphoSitePlus, proteomescout, UniProt)	General overview of *HOX* protein post-translational modifications in cancer	Framework for understanding *HOX* regulation in various cancers, including GBM	[60]
HOXA4	In silico (TCGA, CGGA)	*HOXA4* overexpression in glioma correlates with worse clinical outcomes	Possible adverse prognostic biomarker for GBM	[61]
HOXB7	In silico (CGGA, Ditan Hospital) + IHC	*HOXB7* overexpression in GBM correlates with decreased survival; reduced in 1p/19q-codeleted gliomas	Biomarker to differentiate subtypes; potential oncogenic driver in GBM	[63]
HOXA family	In silico (TCGA, CGGA)	*HOXA*-based distinguish GBM subtypes and predict patient survival	Nomogram using *HOXA* expression could guide personalized therapy	[62]

This table includes the first author's name, year of publication, dataset, *HOX* cluster name, and short references of the related articles. Abbreviations: European Bioinformatics Institute (EBI) Array Express data, Chinese Glioma Genome Atlas (CGGA) data, Gene Expression Omnibus (GEO) data, the Directors Challenge Consortium dataset (DCC), the Japan—National Cancer Center Research Institute (J-NCC), the Genotype Tissue Expression (GTEx) databases

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4.1 *HOXA* family in GBM

HOXA genes play a pivotal role in the progression and prognosis of GBM and lower-grade gliomas (LGG) which refer to gliomas that were classified as grade 2 or grade 3 according to the 2016 CNS4 WHO grading classification system. Studies have consistently shown that 11 *HOXAs* (*HOXA1* to *HOXA11*, and *HOXA13*) are markedly upregulated in both GBM and LGG tissues [49]. This upregulation is strongly associated with advanced tumor stages, *IDH* mutation status, 1p/19q co-deletion, histological subtypes, and unfavorable primary therapy outcomes. Functionally, the *HOXA* genes contribute to GBM progression by driving key oncogenic processes such as cell proliferation, invasion, metastasis, and metabolic reprogramming. Moreover, their elevated expression correlates with reduced overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS) in LGG and GBM patients, highlighting their potential as prognostic biomarkers and therapeutic targets in GBM [52].

A recent study by Zheng et al. [62] developed and evaluated a HOXA-based survival prediction model using various statistical tools. The study found that *HOXA* gene alterations and mRNA expression levels have prognostic significance, with *HOXA1-7*, *HOXA9*, and *HOXA13* distinguishing IDH-mutant and molecular GBM subtypes. Additionally, *HOXA1*, *HOXA2*, *HOXA3*, and *HOXA10* were independently identified as prognostic markers, with their high expression confirmed in clinical GBM tissues. The *HOXA*-based nomogram model demonstrated strong predictive performance ($p = 2.233e-09$) and was validated in both training and validation cohorts. These findings underscore the diagnostic value of the *HOXA* family and the utility of this model in predicting GBM patient survival [62].

The prognostic significance of *HOXA* genes in GBM extends beyond survival prediction models to their functional roles in tumor progression and metabolism. *HOXA3*, in particular, has been implicated in regulating glycolytic metabolism, a key driver of GBM growth. Yang et al. [57] investigated HOXA3's role using knockdown and overexpression models, demonstrating that it influences cell proliferation, tumor formation, and aerobic glycolysis. Chromatin immunoprecipitation, luciferase assays, and western blotting confirmed that HOXA3 directly regulates glycolytic genes HK2 and PKM2, while PLA, immunoprecipitation, and GST pull-down assays identified *KDM6A* as a critical cofactor. Mechanistically, *HOXA3* transcriptionally activates *KDM6A*, which then recruits it to glycolytic gene promoters, facilitating H3K27 demethylation and leading to enhanced aerobic glycolysis and tumor growth. These findings highlight a novel *HOXA3-KDM6A* regulatory axis, linking *HOX* gene-mediated transcriptional activation to GBM metabolism and progression. Building on the role of *HOX* genes in GBM progression, *HOXA5* has been identified as a key driver of glioma aggressiveness, particularly in tumors with chromosome 7 gain. Cimino et al. [7] analyzed TCGA datasets and found that *HOXA5* expression correlates with chromosome 7 amplification, a hallmark of more aggressive glioma subtypes. To investigate its functional role, they used a PDGF-driven proneural GBM mouse model, demonstrating that elevated *HOXA5* expression promotes tumor proliferation and resistance to radiotherapy. High *HOXA5* levels were also linked to shortened survival in both human ($p = 0.003$) and mouse ($p < 0.001$) GBM models, with increased expression observed in recurrent tumors following radiotherapy. These findings suggest that *HOXA5* contributes to glioma genesis by driving chromosome 7 gain and enhancing treatment resistance, further reinforcing the oncogenic role of *HOX* genes in GBM.

Further highlighting the oncogenic role of *HOX* genes in GBM, *HOXA9* has been shown to promote tumor cell survival and therapy resistance. Costa et al. [8] demonstrated that *HOXA9* inhibits apoptosis, enhances proliferation, and confers resistance to tumor necrosis factor-related apoptosis-inducing ligands (TRAIL). Survival analysis revealed that abnormal *HOXA9* expression is independently associated with shorter overall and progression-free survival in GBM patients, and its predictive accuracy improves when combined with MGMT promoter methylation status. The study also found that *HOXA9* activation is driven by or phosphoinositide 3-kinase (PI3K) signaling, establishing it as an autonomous, unfavorable prognostic factor in GBM. Notably, this activation was reversible through epigenetic mechanisms, suggesting potential therapeutic strategies targeting PI3K pathway to modulate oncogenic *HOXA* expression.

Building on *HOXA9*'s role in tumor survival and PI3K signaling, further studies have revealed its broader oncogenic potential in GBM progression, therapy resistance, and molecular regulation. Pojo et al. [40] confirmed *HOXA9* as a prognostic factor associated with shorter survival, identifying its regulation of genes involved in proliferation, DNA repair, and stem cell maintenance. Functionally, *HOXA9* enhances cell viability, invasion, and stemness while inhibiting apoptosis, contributing to GBM aggressiveness. Notably, *HOXA9* promotes TMZ resistance via BCL2 upregulation, highlighting the HOXA9-BCL2 axis as a potential therapeutic target. Further supporting *HOXA9*'s oncogenic role, Goncalves et al. (2020) identified *HOXA9* as a transcriptional regulator of WNT6, activating the WNT/β-catenin pathway in GBM. Gene set enrichment analysis (GSEA) and reporter assays confirmed a significant correlation between *HOXA9*

and *WNT6* expression in glioma patient cohorts, findings that were validated both in vitro and in vivo. Clinically, high *WNT6* expression predicts poor survival in GBM, independent of *HOXA9* levels, while co-expression of *HOXA9* and *WNT6* identifies a subgroup with particularly poor prognosis. This HOXA9-WNT6 regulatory axis establishes WNT signaling as a critical driver of GBM progression, reinforcing its potential as a therapeutic target.

The dysregulated expression of *HOX* genes in GBM is closely linked to therapy resistance and glioma-initiating cell proliferation [23]. Notably, hypermethylation of the HOXA locus at 7p15.2, a hallmark of GBM, correlates with chromosome 7 gain, potentially serving as a compensatory mechanism to regulate gene dosage. However, within this cluster, a CpG island in the *HOXA10* alternative promoter remains unmethylated in HOX-high GBM cases, allowing persistent *HOXA10* overexpression. This suggests that copy number variations at 7p15.2 and DNA methylation at key regulatory CpGs collectively influence *HOXA10* expression. Further analysis of GBM-derived spheres revealed a strong correlation between methylation status and chromatin accessibility, distinguishing HOX-high and HOX-low glioma subtypes. Kurscheid et al. propose that chromosome 7 gain and epigenetic modifications evolve together, orchestrating a HOXA10-driven transcriptional program that fuels GBM progression.

4.2 *HOXB* family in GBM

HOXB1 exhibits context-dependent roles in cancer, it can act as either a tumor suppressor or an oncogene depending on the cancer type and cellular context. In a study by Han et al. [19], the expression profile of *HOXB1* was meticulously examined in human glioma tissues from two comprehensive gene expression datasets CGGA and Gene Expression Omnibus (GEO). Their analysis unveiled a marked decrease in *HOXB1* expression in high-grade glioma tissues (HGG), encompassing WHO grade 3 anaplastic astrocytomas and WHO grade 4 GBM, compared to LGG tissues. To corroborate these findings, further investigations employing quantitative real-time polymerase chain reaction (qRT-PCR) and immunohistochemical analyses were conducted on eight nonneoplastic brain tissues and 40 glioma tissues. The results showed a significant reduction in HOXB1 protein expression in glioma tissues compared to controls. Interestingly, while mRNA levels did not differ significantly between LGG (WHO Grades 1–2) and HGG (Grades 3–4) ($P = 0.069$), immunohistochemistry revealed clear HOXB1 downregulation in HGG suggesting a potential tumor-suppressive role.

In contrast, Li et al. (2020) found HOXB2 to be elevated in GBM patient samples and cell lines (U251, U-87MG, GOS-3) compared to normal human embryonic brain (HEB) cells, with high HOXB2 expression correlating with poor prognosis. Functional studies further demonstrated that HOXB2 knockdown reduced p-PI3K and p-AKT levels, indicating its role in GBM progression via PI3K/AKT signaling and highlighting its potential as a therapeutic target. Building on these findings, Xu et al. [55] reported that *HOXB3* was highly expressed in malignant glioma tissue but absent in normal brain tissue. Using U87 MG and U251 MG cell lines, they confirmed elevated HOXB3 levels, which promoted cell proliferation and invasion, further supporting the oncogenic role of *HOX* genes in GBM progression. Additionally, Xu et al. [53] found that GBM exhibited the highest levels of *HOXB5* expression, a result further validated using the CGGA_325 dataset consists of 325 glioma samples from CGGA subset.

High *HOXB7* expression at both mRNA and protein levels correlates with tumor aggressiveness and reduced survival rates, reinforcing its oncogenic role in GBM [25]. Gliomas with 1p/19q codeletion, particularly oligodendrogliomas, exhibit significantly lower *HOXB7* expression at both the mRNA and protein levels compared to other glioma subtypes, including GBM, highlighting its potential role in tumor progression [63]. Similarly, *HOXB8* has been identified as a driver of GBM aggressiveness. Ma et al. [34] analyzed publicly available RNA sequencing data and patient cohorts, confirming elevated *HOXB8* expression in GBM tumors. Higher *HOXB8* levels correlate with advanced tumor grade and poorer overall survival. Functionally, *HOXB8* promotes GBM cell proliferation and migration while activating the PI3K/AKT pathway and epithelial-mesenchymal transition-related genes. Mechanistically, it may exert these effects by binding to the SAMD9 promoter, facilitating its transcriptional activation.

Like other *HOXB* family members, *HOXB9* may play a key role in glioma progression [12]. Extending this trend, *HOXB13*, linked to various cancers, has also been implicated in GBM. Wang et al. [50] reported its overexpression in GBM tissues, correlating with poor prognosis. Functional studies showed that increased *HOXB13* levels enhance GBM cell proliferation, migration, and invasion, highlighting its potential as a prognostic marker and therapeutic target.

4.3 *HOXC* family in GBM

The *HOXC* gene family plays multifaceted roles in GBM, influencing both tumor progression and the immune microenvironment. In addition to *HOXC4* members, other *HOX* genes such as *HOXA9*, *HOXA10* and *HOXD9* have emerged as

promising biomarkers and therapeutic targets for GBM [1]. Addition key members such as *HOXC6*, *HOXC8*, *HOXC10*, and *HOXC13* serve as critical diagnostic and prognostic biomarkers, with their overexpression correlating with poor patient outcomes [59]. Additionally, their involvement in immune cell infiltration and transcriptional regulation underscores their significance in modulating GBM biology and highlights their potential as therapeutic targets for future interventions. Furthermore, studies by Guan et al. in (2019) and Yang et al. in (2019) underscore the regulatory roles of *HOXC6* and *HOXC10* overexpression in GBM cell proliferation and migration, mediated through the MAPK and PI3K/AKT signaling pathways, respectively [17, 57].

In a recent publication by Li et al. in (2022), utilizing multivariate Cox and stratification analysis unveiled *HOXC6* as a distinct prognostic factor in GBM, even after adjusting for various clinical covariates [30]. Bioinformatic analysis hinted at *HOXC6*'s involvement in cell cycle-related processes, further validated through tumor cell biology experiments, emphasizing its potential as a biomarker gene for tailoring personalized GBM treatment strategies. Similarly, Xuan et al. [56] conducted Kaplan–Meier analysis to assess the prognostic value of *HOXC9* in GBM, revealing its association with poor prognosis. Functional assays elucidated *HOXC9*'s oncogenic role in GBM, with knockdown resulting in decreased cell viability, migration, invasion, and tumorigenicity, while inducing autophagy through the DAPK1-Beclin1 pathway.

Guan et al. [17] analyzed *HOXC10* expression levels and its prognostic implications in GBM tissues, revealing its association with poor prognosis. Knockdown experiments in U87 cells further supported *HOXC10*'s role in promoting cell proliferation, migration, and invasion via activation of the PI3K/AKT pathway. Moreover, Wang et al. (2019a, b) identified *HOXC11* as a risk factor gene for GBM, while Yu et al. [59] elucidated the diagnostic and prognostic significance of *HOXC6*, *HOXC8*, *HOXC10*, and *HOXC13* in GBM through comprehensive analyses integrating RNA-sequencing data and immunohistochemistry. These studies shed light on the multifaceted roles of *HOXC* genes in GBM pathogenesis and underscore their potential as therapeutic targets and prognostic markers.

4.4 *HOXD* family in GBM

The *HOXD* gene family contributes to GBM pathogenesis through transcriptional regulation, epigenetic modifications, and metabolic reprogramming, making them potential biomarkers and therapeutic targets. In cell lines derived from GBM (U-118, U-138) and normal human astrocytes, Guo et al. [18] discovered the expression of *HOXC8*, *HOXC10*, *HOXD1*, *HOXD4*, *HOXD9*, *HOXD10*, and *HOXD13*, contrasting with their absence in healthy tissue. A recent investigation by Deforzh et al. [10] unveiled the intricate connection between two lengthy non-coding RNAs (lncRNAs) and a distant enhancer of the gene promoter of *HOXD3* and *HOXD4*/miR-10b. This linkage activates transcription, thereby targeting miR-10b in GBM for potential therapeutic interventions. Interestingly, while GEPIA (Gene expression profiling interaction analysis) reported an upregulation of *HOXD10* mRNA in GBM, Li et al. [29] observed a downregulation of *HOXD10* protein expression in GBM samples obtained from patients, as indicated by immunohistochemistry analysis**.** Inconsistencies have been observed between transcriptomic and proteomic data, where mRNA overexpression does not always align with corresponding protein expression. For example, although bioinformatics analyses (e.g., GEPIA) have indicated elevated *HOXD10* mRNA levels in GBM, protein expression analysis in patient-derived samples [29] revealed a significant downregulation. These discrepancies highlight the necessity for multi-level validation across independent datasets to achieve a clearer understanding of gene expression dynamics in GBM. Moreover, Li et al. conducted GO and KEGG enrichment analyses, which suggested that *HOXD10* expression primarily participates in cytokine-cytokine receptor interactions, shedding light on its potential role in GBM pathogenesis. Furthermore, Shinawi et al. [45] identified a collection of CpG sites exhibiting distinctive hypermethylation levels between short-term survival and long-term survival cases of GBM patients. This set of CpG loci includes *HOXD8*, *HOXD13*, and *HOXC4*, the transcription factors NR2F2 and TFAP2A, as well as Dickkopf 2, a negative regulator of the WNT/β-catenin signaling pathway.

Xu et al. [54] investigated *HOXD9* in GBM under hypoxic conditions, revealing its role in promoting glycolysis and tumor growth by activating PFKFB3 and enhancing HMGB1 secretion. High *HOXD9* expression correlated with poor survival, while its silencing reduced tumor mass, partially rescued by *PFKFB3* overexpression. These findings highlight the *HOXD9*/*PFKFB3* axis as a key driver of GBM progression and a potential therapeutic target.

Supporting this, Roura et al. [43] identified transcription factor binding sites in chromatin regions, suggesting a regulatory role in glioma progression. Hierarchical clustering analysis of TCGA GBM data revealed 64 transcription factor genes altered in WHO Grade 4 GBM, with a subset also elevated in lower-grade gliomas. Notably, *HOXD9*, *HOXD11*, *HOXC10*, *HOXC11*, *HOXC6*, *HOXB3*, *HOXA2*, and *HOXA1* showed significant overexpression in GBM, further implicating *HOX* genes in glioma pathogenesis.

5 Discussion

GBM remains the most aggressive and lethal primary brain tumor, with *HOX* gene dysregulation playing a crucial role in its progression, prognosis, and therapy resistance. *HOX* genes, typically silenced in adult tissues, are reactivated in various cancers, including GBM, where they contribute to tumor initiation, proliferation, invasion, and treatment resistance [8, 16].

The *HOXA* gene cluster, particularly *HOXA1*, *HOXA2*, *HOXA3*, and *HOXA4*, is highly expressed in GBM and correlates with tumor progression and poor survival [49]. Their regulatory roles extend to oncogenic pathways, metabolic reprogramming, and treatment resistance, making them promising therapeutic targets. Among them, *HOXA1* is regulated by lncRNA-HOTAIRM1, which influences GBM proliferation and invasion through epigenetic mechanisms [27]. Additionally, *HOXA10* has been implicated in homologous recombination repair and TMZ resistance, highlighting its role in therapy response [21].

The *HOXB* family also contributes to glioma genesis, with *HOXB7* and *HOXB8* driving GBM aggressiveness through activation of oncogenic pathways such as PI3K/AKT [34]. *HOXB9* and *HOXB13* have been linked to GBM progression, with their elevated expression associated with increased proliferation, migration, and poor prognosis [12, 50, 51].

The *HOXC* gene cluster plays multifaceted roles in GBM, influencing both tumor progression and the immune microenvironment [10]. *HOXC6*, *HOXC8*, *HOXC10*, and *HOXC13* serve as critical diagnostic and prognostic markers, with their overexpression linked to poor patient outcomes [57]. Notably, *HOXC10* promotes GBM progression via PI3K/AKT signaling, while *HOXC9* has been identified as a key regulator of tumor growth and autophagy [54].

The *HOXD* gene family is also implicated in GBM, with multiple members showing altered expression [18]. *HOXD9* has been identified as a key driver of GBM under hypoxic conditions, enhancing glycolysis and tumor growth via transcriptional activation of PFKFB3 [54]. Other *HOXD* genes, such as *HOXD10*, exhibit differential expression at the mRNA and protein levels, suggesting complex regulatory mechanisms that may influence tumor behavior and therapeutic response [29].

HOX gene dysregulation in GBM is frequently linked to epigenetic alterations, including DNA hypermethylation, H3K27me3 loss, and chromosomal gains, particularly on chromosome 7, which harbors the *HOXA* cluster [9, 23]. These changes contribute to aberrant *HOX* expression patterns and tumor heterogeneity. Loss of H3K27me3 has been identified as a key driver of transcriptional alterations in GBM, further emphasizing the role of epigenetic modifications in *HOX* gene regulation [24].

Despite strong evidence supporting the oncogenic role of *HOX* genes in GBM, some studies suggest that certain *HOX* family members may also exhibit tumor-suppressive functions. One possible explanation for these conflicting findings is that RNA expression does not always correlate with protein levels, yet most studies primarily rely on bulk RNA-seq data, while protein-level analyses remain less frequently examined. For example, HOXB1 protein is downregulated in high-grade gliomas, despite no significant changes in mRNA expression, suggesting a potential tumor-suppressive role [19, 39]. These discrepancies highlight the context-dependent nature of *HOX* gene functions, which may be influenced by tissue specificity, cell lineage differences, and methodological factors, including bulk RNA-seq vs. single-cell analyses or differences between in vitro and in vivo models. Addressing these gaps through comprehensive, multi-level investigations will be essential for clarifying the diverse roles of *HOX* genes in glioma pathogenesis.

Emerging evidence further suggests that *HOX* gene dysregulation in GBM is not uniform but may vary according to molecular subtypes, adding another layer of complexity to their role in glioma progression. For instance, Mesenchymal GBM, known for its high invasiveness and cellular plasticity, frequently exhibits upregulation of *HOXA9* and *HOXA10,* which are implicated in epithelial–mesenchymal transition (EMT) and tumor aggressiveness, as illustrated in Fig. 2 [21, 40]. In contrast, while direct evidence linking *HOXB* and *HOXD* genes to the proneural subtype remains limited, their established roles in neural differentiation suggest they may contribute to the proneural phenotype. Additionally, Classical GBM is frequently associated with chromosomal alterations, such as HOXA5 amplification on chromosome 7, which may support tumor proliferation and maintenance of the classical tumor phenotype [7, 20].

Further stratification of *HOX* gene dysregulation by molecular subtypes is crucial for refining prognostic models and guiding subtype-specific therapeutic strategies. By integrating molecular classification with *HOX* gene expression patterns, future research can provide a more nuanced understanding of GBM heterogeneity, ultimately paving the way for more targeted and effective treatments.

Although numerous studies have highlighted the potential of *HOX* genes as biomarkers in GBM, critical questions remain regarding their specificity, sensitivity, and prognostic value compared to established markers such as MGMT

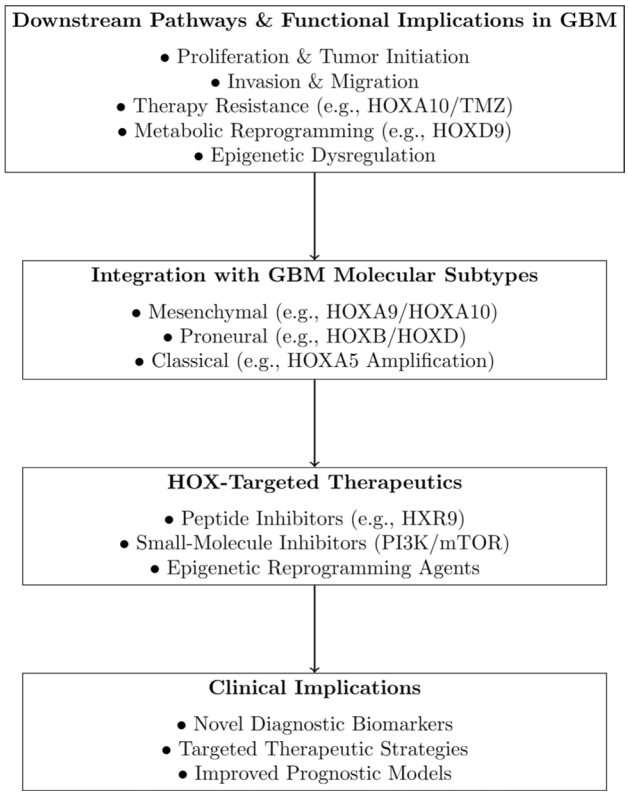

Fig. 2 This diagram illustrates the central role of *HOX* gene dysregulation in GBM, depicting its impact on downstream pathways (proliferation, invasion, therapy resistance, metabolic reprogramming, and epigenetic alterations) and its integration with GBM molecular subtypes (mesenchymal, proneural, and classical). The figure also highlights HOX-targeted therapeutic strategies and their clinical implications, including potential biomarkers and therapies

promoter methylation and TERT promoter mutations. For instance, *HOXC6* has been proposed as a diagnostic marker for GBM, but its expression is not exclusive to GBM and is also observed in other HGGs, suggesting a broader role in glioma biology [57]. Independent validation across multiple datasets has demonstrated that *HOXA11*, *HOXB8*, *HOXA9*, and *HOXA13* consistently correlate with poor patient outcomes [8, 11, 34, 44]. Notably, *HOXA9* expression correlates with poor prognosis, independent of MGMT promoter methylation status, suggesting it may serve as an additional prognostic marker. Combining *HOXA9* expression with MGMT methylation and other conventional prognostic markers could enhance predictive accuracy and improve risk stratification models [8].

Future studies should prioritize large-scale, independent validation efforts to establish HOX-based gene signatures as robust diagnostic and prognostic tools in clinical practice. Integrating *HOX* gene expression with established molecular markers could refine personalized treatment approaches and improve GBM patient outcomes.

Beyond their diagnostic potential, *HOX* genes also hold promise as therapeutic targets due to their strong association with tumor progression and therapy resistance. One promising approach involves HOX-PBX inhibitors, such as HXR9 and HTL-001, which disrupt HOX–PBX dimer formation and have demonstrated preclinical efficacy in multiple cancer models by inhibiting tumor proliferation and inducing apoptosis [1, 35]. Additionally, in HOXA9-driven GBM, targeting downstream signaling pathways, particularly the PI3K/mTOR axis, with small-molecule inhibitors has shown potential in blocking survival signals and limiting tumor progression [28].

Furthermore, epigenetic reprogramming strategies, including DNA methyltransferase inhibitors and histone deacetylase inhibitors, offer another promising avenue for restoring normal *HOX* gene expression patterns [38]. These strategies not only reduce tumor aggressiveness but may also enhance the efficacy of conventional therapies. Future research should focus on integrating multi-omics approaches and further evaluating *HOX* gene-targeted therapies to improve GBM prognosis and treatment outcomes [35].

6 Conclusion

This review provides a comprehensive summary of research findings up to the end of 2024 on the role of *HOX* gene clusters in GBM initiation, progression, prognosis, and treatment response. We have systematically organized findings related to the *HOXA*, *HOXB*, *HOXC*, and *HOXD* clusters, covering 34 of the 39 *HOX* genes in GBM, with the exception of *HOXA7*,

HOXB4, *HOXB6*, *HOXC5*, and *HOXC12*, for which no reliable studies were identified (Table 1). By consolidating existing knowledge, this review highlights the current understanding of *HOX* gene involvement in GBM and underscores their potential as biomarkers and therapeutic targets. Future research will be crucial in refining GBM subtypes and advancing targeted treatment strategies.

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Declarations

Ethics approval and consent to participate Not applicable.

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