Majid Ghasemian1, Masoumeh Rajabibazl1,*, Unes Sahebi1, Samira Sadeghi2, Reza Malek1, Veys Hashemnia3 and Reza Mirfakhraie3,4*

Abstract
MIR4435-2HG (LINC00978) is a long non-coding RNA (lncRNA) that acts as an oncogene in almost all cancers. This lncRNA participates in the molecular cascades involved in other disorders such as coronary artery diseases, osteoarthritis, osteoporosis, and periodontitis. MIR4435-2HG exerts its functions via the spectrum of different mechanisms, including inhibition of apoptosis, sponging microRNAs (miRNAs), promoting cell proliferation, increasing cell invasion and migration, and enhancing epithelial to mesenchymal transition (EMT). MIR4435-2HG can regulate several signaling pathways, including Wnt, TGF-β/SMAD, Nrf2/HO-1, PI3K/AKT, MAPK/ERK, and FAK/AKT/β-catenin signaling pathways; therefore, it can lead to tumor progression. In the present review, we aimed to discuss the potential roles of lncRNA MIR4435-2HG in developing cancerous and non-cancerous conditions. Due to its pivotal role in different disorders, this lncRNA can serve as a potential biomarker in future investigations. Moreover, it may serve as a potential therapeutic target for the treatment of various diseases.

Keywords: MIR4435-2HG, lncRNA, Cancer, Biomarker

Introduction
Genetic alterations are one of the primary causes of cancer, leading to the deregulation of gene networks [1–3]. In recent years following developments in RNA sequencing technologies, this insight came into being that a large part of the genome transcribes into non-protein-coding RNAs [4]. Long non-coding RNAs (lncRNAs) are a subclass of functional RNAs which are longer than 200 nucleotides in sequence length without a protein-coding capacity [5–7]. In the beginning, lncRNA transcripts were regarded as ‘transcriptional noise’ or ‘junk’. Subsequent investigations revealed that lncRNAs are key players in human disorders, particularly in malignant conditions [8, 9]. Although lncRNAs do not translate into proteins, they play a meaningful function in regulating gene expression through different mechanisms such as remodeling of chromatin, modulating the activity of transcription factors, epigenetic regulation, post-transcriptional, and cell cycle regulation [10, 11].

MIR4435-2 Host Gene (MIR4435-2HG), also named LINC00978, AK001796, AWPPH, MIR4435-1HG, MORRBID, and AGD2, is an lncRNA that resides on chromosome 2q13 region and includes ten exons. MIR4435-2HG has 108 transcripts produced through alternative splicing (https://www.ensembl.org/Homo_sapiens/Gene/Summary?db=core;g=ENSG00000172965;r=2:111006015-111523376). Previous studies have reported that the MIR4435-2HG has an oncogenic role in the progression of different cancer types. In addition to the role of MIR4435-2HG in tumorigenesis, some studies

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suggest that it is involved in the pathogenesis of non-cancerous conditions such as coronary artery diseases [12], osteonecrosis [13], osteoarthritis [14], osteoporosis [15], and periodontitis [16]. Due to the important regulatory roles of \( \text{MIR4435-2HG} \), in the present review, we provide comprehensive information about its function in cancer and other diseases.

**MIR4435-2HG and cancer**

Previous studies have shown that the expression level of \( \text{MIR4435-2HG} \) was upregulated in almost all cancers. \( \text{MIR4435-2HG} \) upregulation can promote tumor progression by increasing cell proliferation, invasion, migration, epithelial-mesenchymal transition (EMT), chemoresistance and suppression of apoptosis.

**Colorectal cancer (CRC)**

Overexpression of \( \text{MIR4435-2HG} \) has been reported in CRC tissues and cell lines in several studies [17–22]. Wen et al. have demonstrated that upregulation of \( \text{MIR4435-2HG} \) in CRC tissues was significantly correlated with the TNM stage [17]. Cancer-developing conditions such as chemoresistance, invasion, metastasis, migration, cancer stemness, and EMT can be regulated by Yes-related protein 1 (YAP1) transcription factor [23]. Dong et al. showed that \( \text{MIR4435-2HG} \) could regulate the expression of \( \text{miR-206} \). On the other hand, they also indicated that \( \text{YAP1} \) was a potential target for \( \text{miR-206} \) (Fig. 1 and Table 1). \( \text{MIR4435-2HG} \) knockdown could block invasion, migration, and cell proliferation through the miR-206/YAP1 axis in the HCT116 and SW620 cell lines [18]. Previous studies reported that expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and its regulator, heme oxygenase-1 (HO-1), increased after treating cancer cells with chemotherapeutic agents. These factors regulate the detoxification process and antioxidant enzymes, which results in the reduction of drug effects and an increase in drug resistance [24, 25]. In HCT116R cells (a cisplatin-resistant cell line), knockdown of \( \text{MIR4435-2HG} \) significantly induced cisplatin sensitivity, enhanced apoptosis, and inhibited cell proliferation via modulating Nrf2/HO-1 cascade (Fig. 1). Hence, it seems that \( \text{MIR4435-2HG} \) is involved in oxidative stress [19]. Another experiment has indicated that in patients with colon cancer, serum levels of glucose transporter 1 (GLUT-1) and \( \text{MIR4435-2HG} \) were significantly higher than healthy controls. Moreover, silencing \( \text{MIR4435-2HG} \) inhibits cell proliferation through down-regulation of GLUT-1 in the HT-29 cancerous cell line (Fig. 1) [20]. In our previous study, we showed a positive correlation between \( \text{β-catenin} \) and \( \text{MIR4435-2HG} \) expression that indicated mentioned lncRNA might regulate the Wnt signaling pathway via stabilization of \( \text{β-catenin} \), which can lead to the progression of CRC [21]. Shen et al. showed that high expression of \( \text{MIR4435-2HG} \) was remarkably related to clinicopathological features, including stage, tumor size, tumor node and lymph node metastasis. Their results showed that the patients

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**Fig. 1** Schematic representation of \( \text{MIR4435-2HG} \) functions in CRC. Increased level of \( \text{MIR4435-2HG} \) blocks \( \text{miR-206} \) which leads to elevation of \( \text{YAP1} \) and enhanced cell invasion, migration, proliferation and chemoresistance. In HCT116R cells, the activation of Nrf2 pathway leads to drug resistance; however, knockdown of \( \text{MIR4435-2HG} \) sensetives cancer cell to chemotherapy through inhibition of Nrf2. Furthermore, \( \text{MIR4435-2HG} \) can increase CRC progression via promoted GLUT-1.
Table 1. *MIR4435-2HG* participates in the pathogenesis of different cancers via the regulation of different miRNAs (Δ: knock-down, EMT: Epithelial-Mesenchymal Transition, TNBC: Triple-negative breast cancer, NSCLC: non-small cell lung cancer, HNSCC: head and neck squamous cell carcinoma).

| Cancer type   | MIR4435-2HG | miRNA   | Target gene | Function | References |
|---------------|-------------|---------|-------------|----------|------------|
| Colorectal cancer | Up-regulated | ↓miR-206 | ↑YAP1       | Δ MIR4435-2HG: ↓Invasion, ↓Migration, ↓Cell proliferation, ↓MT, ↓CRC growth, ↑Liver metastasis | [18] |
| Gastric cancer  | Up-regulated | ↓miR-497 | ↑NTRK3      | Δ MIR4435-2HG: ↓Cell proliferation, ↓Metastasis, ↑Apoptosis | [28] |
| Gastric cancer  | Up-regulated | ↓miR-138-5p | ↑SOX4      | Δ MIR4435-2HG: ↓Invasion, ↓Migration, ↓Cell proliferation, ↓EMT, ↑Apoptosis, ↑Tumor growth | [29] |
| Hepatocellular carcinoma | Up-regulated | ↑miRNA-487a | –   | Δ MIR4435-2HG: ↑Cell proliferation, ↑Migration | [35] |
| Hepatocellular carcinoma | Up-regulated | ↓miR-136-5p | ↑B3GN5    | Δ MIR4435-2HG: ↓Invasion, ↓Migration, ↓Cell proliferation, ↑Apoptosis | [38] |
| NSCLC          | Up-regulated | ↓miR-6754-5p | –   | Δ MIR4435-2HG: ↓Invasion, ↓Migration, ↓Cell proliferation, ↑Apoptosis | [45] |
| Breast cancer   | Up-regulated | ↓miR-22-3p | ↑TMEM98    | Δ MIR4435-2HG: ↑viability, ↓Invasion, ↓Migration, ↓Cell proliferation, ↑EMT | [48] |
| Ovarian cancer  | Up-regulated | ↓miR-128-3p | ↑CDK14     | Δ MIR4435-2HG: ↓Cell proliferation, ↓Invasion, ↓Migration, ↓Tumor growth, ↑Apoptosis | [51] |
| Glioma cancer   | Up-regulated | ↓miR-1224-5p | ↑TGFBR2   | Δ MIR4435-2HG: ↓Cell proliferation, ↓Invasion, ↓Tumor growth | [58] |
| Glioma cancer   | Up-regulated | ↓miR-125a-5p | ↑TAZ      | Δ MIR4435-2HG: ↓Migration, ↓Cell proliferation, ↑Apoptosis, ↑Wnt pathway, ↑Tumor volume | [61] |
| Cervical cancer | Up-regulated | ↓miR-128-3p | ↑Msi2      | Δ MIR4435-2HG: ↓Cell proliferation, ↓Invasion, ↓Migration | [66] |
| Bladder cancer  | Up-regulated | ↓miR-4288 | –   | Δ MIR4435-2HG: ↓Cell proliferation, ↓Invasion, ↓Migration | [71] |
| HNSCC          | Up-regulated | ↓miR-383-5p | ↑RBM3     | Δ MIR4435-2HG: ↓Cell proliferation, ↓Invasion, ↓Migration, ↓EMT, ↓Tumor growth | [70] |
| Melanoma       | Up-regulated | ↓miR-802 | ↑FLOT2     | Δ MIR4435-2HG: ↑Cell proliferation, ↑Invasion, ↑Migration | [72] |
| TNBC           | Up-regulated | ↑miRNA-21 | –   | Δ MIR4435-2HG: ↑Cell viability, ↑cell proliferation, ↑chemoresistance | [49] |
| NSCLC          | Up-regulated | ↓miRNA-204 | ↑CDK6     | Δ MIR4435-2HG: ↓cell proliferation, ↓invasion, ↓migration | [46] |

with higher levels of *MIR4435-2HG* had a worse prognosis than the patients with lower expression levels. In addition, *MIR4435-2HG* silencing remarkably reduced cell proliferation and enhanced cell apoptosis [22]. To conclude, *MIR4435-2HG* can promote CRC via different mechanisms.

**Gastric cancer (GC)**

Several studies reported that the expression level of *MIR4435-2HG* was significantly increased in GC tissues, plasma samples, and different cell lines compared to the normal controls [26–29]. TGF-β/SMAD is one of the pathways involved in the progression of metastasis in gastric cancer [30]. Min et al. showed that *MIR4435-2HG* expression was significantly correlated with TNM stage, tumor size, and lymphatic metastasis. Knockdown of *MIR4435-2HG* elevated the expression of E-cadherin protein while the expression levels of vimentin, slug, N-cadherin, and twist proteins were inhibited. On the other hand, *MIR4435-2HG* knockdown leads to the inhibition of transforming growth factor beta (TGF-β) and phosphorylated SMAD2 (p-SMAD2) in gastric cancer cell lines. This observation suggests that knockdown of *MIR4435-2HG* can elevate EMT, and apoptosis and inhibit cell cycle progression, invasion, and migration via the regulation of TGF-β/SMAD signaling pathway (Fig. 2) [27, 31, 32]. Yuan et al. reported that *MIR4435-2HG* could target miR-497. Interestingly, tropomyosin receptor kinase C (NTRK3) plays a critical role in cancer progression and is a direct target of miR-497. *MIR4435-2HG* acts as a molecular sponge of miR-497, which leads to an increase in NTRK3. It can be concluded that the elevation of *MIR4435-2HG* could enhance tumorigenesis via miR-497/NTRK3 axis (Fig. 2 and Table 1) [28]. Gao et al. demonstrated that high expression of *MIR4435-2HG* was associated with poor survival rate in GC patients. They also reported the enhancement of apoptosis and suppression of cell proliferation, migration, invasion and EMT after *MIR4435-2HG* knockout in gastric carcinoma cells. It was suggested that overexpression of *MIR4435-2HG* affects the expression of *SRY-box transcription factor 4* (SOX4) via sponging miR-138-5p. Therefore, *MIR4435-2HG* plays an oncogenic role in GC by targeting the miR-138-5p/ SOX4 axis (Fig. 2 and Table 1) [29].
Hepatocellular carcinoma (HCC)

*MIR4435-2HG* upregulation has also been detected in hepatocellular carcinoma tissues and cell lines. [33–38]. *In vitro* and in vivo studies performed by Zhao et al. showed that upregulation of *MIR4435-2HG* increased migration, cell proliferation, metastasis, and tumor growth in hepatocellular carcinoma cells via regulating the interaction of Y-box binding protein 1 (YBX1) with snail family transcriptional repressor 1 (SNAIL1) and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA). Previous studies reported that YBX1 could induce EMT, SNAIL1 mRNA translation, and promote metastasis. YBX1 can stimulate PIK3CA transcription and enhance the PI3K/AKT signaling pathway by binding its promoter in cancer cells (Fig. 3) [34, 39, 40]. Another study showed that *miRNA-487a* and *MIR4435-2HG* were elevated in HCC tumor samples compared to adjacent tissues, and a positive correlation was detected between the genes expression. The over-expression of *MIR4435-2HG* in the HCC SNU-398 and SNU-182 cell lines promoted cell proliferation through upregulation of *miRNA-487a* (Fig. 3 and Table 1) [35]. Polycomb repressive complex 2 (PRC2) consists of multiple subunits including, Enhancer of Zeste Homolog 2 (EZH2) that displays methyltransferase activity. Previous studies showed that EZH2 was remarkably upregulated in many cancers, including HCC. Using chromatin immunoprecipitation (ChIP), Xueying et al. showed that E-cadherin and p21 are molecular targets of *MIR4435-2HG*. As shown in Fig. 3, *MIR4435-2HG* enhances the promoter methylation of E-cadherin and p21 genes via mediating the accumulation of EZH2 in the promoter region. It can be concluded that *MIR4435-2HG* increases HCC progression via blocking E-cadherin and p21 expression through EZH2-mediated epigenetic silencing (Fig. 3) [36, 41, 42]. Zhang et al. reported that high expression of *MIR4435-2HG* correlates with poor HCC prognosis. They also indicated that *MIR4435-2HG* knockdown strongly induced apoptosis, cell cycle arrest and significantly decreased HCC cell proliferation capacity. Inhibition of *MIR4435-2HG* led to a decrease of phosphorylated JNK (p-JNK), phospho-p38 (p-p38), and phospho-ERK (p-ERK). It seems that *MIR4435-2HG* induces the progression of HCC by activating the MAPK/ERK signaling pathway (Fig. 3) [37]. Zhu et al. identified the target genes of *MIR4435-2HG*. They also confirmed interactions between *MIR4435-2HG*, *miR-136-5p*, and *B3GNT5*, one of the downstream targets of *miR-136-5p*, using luciferase reporter assays. *MiR-136-5p* acts as a tumor suppressor in various cancers such as liver cancer. *MIR4435-2HG* could sponge *miR-136-5p* while the expression of UDP-GlcNAc:betaGal beta-1,3-N-acetylgalactosaminyltransferase 5 (*B3GNT5*) was upregulated in liver cancer tissues. It can be concluded that
MIR4435-2HG, by sponging miR-136-5p, can directly reverse its inhibitory effects on target genes such as B3GNT5, thereby facilitates the progression of liver cancer via the MIR4435-2HG/miR-136-5p/ B3GNT5 axis (Fig. 3 and Table 1) [38].

Lung cancer (LC)
Qiaoyuan et al. showed that the MIR4435-2HG expression was downregulated after treating LC cells with resveratrol. They showed that cell cycle arrest occurred in G0/G1 phase following MIR4435-2HG knockdown. They also indicated that inhibition of MIR4435-2HG in lung cancerous cell lines enhanced the anticancer effects of resveratrol [43]. Another experiment revealed EMT suppression following MIR4435-2HG knockdown. Notably, MIR4435-2HG prevents the destruction of β-catenin by the proteasome system, however, MIR4435-2HG knockdown resulted in the decreased β-catenin transactivation and subsequent inhibition of the Wnt/β-catenin signaling pathway [44]. MIR4435-2HG can potentially sponge miR-6754-5p in non-small cell lung cancer (NSCLC). In NSCLC samples, the miR-6754-5p expression was downregulated and negatively correlated with MIR4435-2HG expression. It can be concluded that the MIR4435-2HG plays an oncogenic role in NSCLC via blocking the miR-6754-5p function (Table 1) [45]. Recently, Wu et al. introduced miR-204 as a target for MIR4435-2HG in NSCLC. MIR4435-2HG leads to the progression of NSCLC through sponging miR-204. Silencing of MIR4435-2HG promoted the expression of miR-204 and therefore decreased the expression of cyclin dependent kinase 6 (CDK6), resulting in the enhancement of cell proliferation, invasion and migration in the A549 cell line [46].

Breast cancer (BC)
One of the pioneer investigations for the assessment of MIR4435-2HG has been conducted in the BC tissues and cell lines by Lin et al. They indicated that MIR4435-2HG was over-expressed in breast cancer tissues and cell lines compared with corresponding controls and therefore may act as an oncogene. They reported that hormone receptor status and MIR4435-2HG expression were negatively correlated [47]. Consistent with the above study, Jing et al. showed that MIR4435-2HG was upregulated in breast cancer tissues and cell lines. They indicated that MIR4435-2HG could enhance many cellular parameters such as proliferation, EMT, migration, and invasion via regulating the miR-22-3p/TMEM9B axis (Fig. 4 and Table 1) [48]. Liu et al. demonstrated that the plasma level of MIR4435-2HG was remarkably higher in patients with Triple-negative breast cancer (TNBC) than healthy
controls, and its expression level was positively correlated to miR-21. It was concluded that overexpression of MIR4435-2HG increased cell viability, proliferation and induced chemoresistance via interaction with miR-21 in MDA-MB-231 and BT-20 cell lines [49].

**Ovarian cancer (OC)**

It has been shown that MIR4435-2HG was upregulated in OC tissues and cell lines [50, 51]. It is suggested that MIR4435-2HG can distinguish stage I and II OC patients from healthy controls. Gong et al. reported that the expression level of TGF-β1 was upregulated in OC tissues and positively correlated with MIR4435-2HG expression. Using in vitro studies, they indicated the overexpression of MIR4435-2HG in UWB1.289 and UWB1.289 + BRCA1 cells led to upregulation of TGF-β1. Taken together, MIR4435-2HG could increase OC progression through overexpression of TGF-β1 (Fig. 4) [50]. Lijuan et al. indicated that the MIR4435-2HG and cyclin dependent kinase 14 (CDK14) were upregulated while miR-128-3p was down-regulated in cell lines and OC tissue samples. On the other hand, the expression of MIR4435-2HG was negatively associated with miR-128-3p in OC tissue. They showed that MIR4435-2HG could target miR-128-3p therefore, it might be concluded that MIR4435-2HG acts as the miR-128-3p sponge. CDK14 is a downstream target of miR-128-3p. In vitro studies confirmed that miR-128-3p targeted CDK14 and suppressed its expression. Knockdown of MIR4435-2HG promoted the expression of miR-128-3p, which led to decreased CDK14 expression (Fig. 4 and Table 1) [51].

**Prostate cancer (PC)**

The expression level of MIR4435-2HG is reported to be enhanced in prostate cancer. It is suggested that this lncRNA causes cancer progression through various mechanisms such as FAK/AKT/β-catenin and TGF-β1 pathways [52, 53]. Moreover, overexpression of ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 1 (ST8SIA1) can increase the tumor cell proliferation, migration, and invasion in prostate cancer, colorectal cancer, and breast cancer via the promotion of the FAK-AKT/mTOR signaling pathway [52, 54, 55]. Knockdown of MIR4435-2HG suppressed cell proliferation, invasion, and migration by blocking the activation of the FAK/AKT/β-catenin pathway in PC cell lines. Xing et al. indicated that knockdown of ST8SIA1 suppressed the effects of MIR4435-2HG in tumor progression. It seems that MIR4435-2HG contributes to tumorigenesis via the MIR4435-2HG/ST8SIA1 axis [52, 56]. Hui et al. demonstrated that the plasma level of TGF-β1 was remarkably higher in patients with PC than healthy controls.
and TGF-β1 expression level was positively correlated to MIR4435-2HG. They reported that the effects of MIR4435-2HG on cell migration and invasion decreased following the inhibition of TGF-β1 (Fig. 5) [53].

**Glioma cancer**

One of the members of the TGF-β/Smad signaling pathway is transforming growth factor-beta receptor type II (TGFBR2) that acts as a cancer suppressor [57]. Xu et al. reported that the expression level of MIR4435-2HG was upregulated in patients with glioblastoma (GBM). In contrast, the expression level of miR-1224-5p was suppressed in GBM cancer cell lines. They used bioinformatics predictions and in vitro methods to show that this lncRNA acts as a sponge for miR-1224-5p. On the other hand, one of the direct targets of miR-1224-5p is TGFBR2 gene, and the mRNA level of its gene was enhanced in GBM cancer cell lines. Taken together, it can be argued that MIR4435-2HG can promote cancer progression by targeting the miR-1224-5p/TGFBR2 axis (Table 1) [58]. TGF-β signaling pathway is an essential factor for EMT. In patients with glioma cancer, a positive correlation was detected between the plasma levels of TGF-β and MIR4435-2HG. Therefore, it may be concluded that MIR4435-2HG is involved in the progression of glioma occur through TGF-β signaling pathway [59]. As a transcription coactivator, tafazzin, phospholipid-lysophospholipid transacylase (TAZ) is one of the most important downstream effectors of the Hippo signaling pathway that regulates cell proliferation, migration, and apoptosis [60]. The expression level of TAZ was upregulated in the brain tissue of glioma patients. Shen et al. indicated that the expression of MIR4435-2HG was positively correlated with TAZ expression, while miR-125a-5p expression was negatively correlated with TAZ expression in the brain tissue (Table 1) [61].

**Leukemia cancers**

Rho-associated protein kinase 2 (ROCK2) is an important therapeutic target, and its upregulation was confirmed in many cancers, including T-cell acute lymphoblastic leukemia (T-ALL) [62, 63]. The expression of MIR4435-2HG and ROCK2 was positively correlated in patients with T-ALL. The overexpression of MIR4435-2HG remarkably increased ROCK2 expression at both protein and mRNA levels; also, the overexpression of ROCK2 significantly upregulated MIR4435-2HG expression in T-ALL cells. It seems that MIR4435-2HG inhibits apoptosis

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**Fig. 5** MIR4435-2HG contributes to the pathogenesis of prostate cancer via different mechanisms. Elevation of MIR4435-2HG induces cell proliferation, invasion, migration and activation of TGF-β and FAK/AKT/β-catenin signaling pathways via modulating the expression of MMP2, MMP9, Ki67, Survivin, c-Myc, β-catenin, Cyclin D1, FAK and AKT.
and increases cell proliferation in T-ALL cells through interactions with ROCK2 [64]. Zhigang et al. reported that MIR4435-2HG was overexpressed in human acute myeloid leukemia (AML), which was correlated with a poor survival rate. They showed that MIR4435-2HG acts as a transcriptional repressor of BIM pro-apoptotic gene and, via this mechanism, regulates the lifespan of myeloid cells. In vivo study demonstrated that the loss of MIR4435-2HG in genetic mice models promoted the expression levels of BIM that increased cell death in mature and immature myeloid cells [65].

Other cancers
The overexpression of MIR4435-2HG has also been reported in other cancers, including cervical cancer (CC) [66], clear cell renal cell carcinoma (ccRCC) [67, 68], esophageal squamous cell (ESCC) [69], head and neck squamous cell carcinoma (HNSCC) [70], bladder cancer (BCa) [71], melanoma [72] and nasopharyngeal carcinoma (NPC) [73].

MIR4435-2HG could target miR-128-3p and negatively modulated its expression in cervical cancer (CC). As shown in Fig. 5d, miR-128-3p negatively regulates the expression level of musashi RNA binding protein 2 (MSI2) gene. Therefore, it can be concluded that knockdown of MIR4435-2HG suppresses migration, invasion, and proliferation of CC cells via regulating the miR-128-3p/MSI2 axis (Table 1) [66]. Jianquan et al. reported that MIR4435-2HG knockdown not only increased apoptosis and cell cycle arrest in G0/G1 phase but also decreased invasion and migration in clear cell renal cell carcinoma [67]. Zhu et al. suggested that MIR4435-2HG could directly interact with miR-513a-5p and repressed its expression in ccRCC. Knockdown of MIR4435-2HG inhibited proliferation, metastasis and tumour progression by downregulating Kruppel like factor 6 (KL6) as the direct target of miR-513a-5p [68].

Knockdown of lncRNA MIR4435-2HG regulates cell cycle, cell proliferation, and cells growth via modulating MDM2/p53 signaling pathway in patients with ESCC [69]. Wang et al. demonstrated that the expression level of MIR4435-2HG was upregulated in BCa tissues and cell lines compared to the control samples. They indicated that MIR4435-2HG served as a competing endogenous RNA (ceRNA) and sponged miR-4288. Using in vitro methods, they showed that knockdown of MIR4435-2HG significantly inhibited tumor growth by sponging miR-4288 [71]. Shu et al. reported that the high expression level of MIR4435-2HG was significantly associated with advanced tumor metastasis node in patients with HNSCC. In vivo and in vitro investigations indicated that knockdown of MIR4435-2HG decreased invasion, cell proliferation, and EMT in HNSCC cancer cell lines. As shown in Table 1, MIR4435-2HG executes these functions via modulating miR-383-5p. On the other hand, one target of miR-383-5p is RNA binding motif protein 3 (RBM3). It can be concluded that HNSCC progression can be regulated by MIR4435-2HG/miR-383-5p/RBM3 axis [70]. It has been established that flotillin-2 (FLOT2) has a critical role in the progression of human cancers through different mechanisms [74, 75]. According to bioinformatics analysis, miR-802 targets FLOT2 gene. Han et al. showed that MIR4435-2HG sponged miR-802 which leads to increased expression of FLOT2 and tumor progression (Table 1) [72]. The experimental studies showed that MIR4435-2HG inhibited apoptosis while facilitating migration, and cell proliferation in NPC cells. The mentioned lncRNA exerts this function by inhibiting of phosphatase and tensin homolog (PTEN) as a tumor suppressor gene [73].

MIR4435-2HG and non-cancerous diseases
Accumulating evidence reveals that MIR4435-2HG not only is involved in cancer progression but also plays a critical role in the development of other diseases. In this section, we investigated the role of MIR4435-2HG in non-cancerous disorders.

Coronary artery diseases (CAD)
The serum level of MIR4435-2HG remarkably increased in CAD patients compared to healthy controls. Clinical studies revealed that treatment with statins drugs, atorvastatin, and rosuvastatin, reduced MIR4435-2HG level significantly in CAD patients. This reduction was mainly observed in patients treated with rosuvastatin [12].

Osteoarthritis
The MIR4435-2HG transcript level was lower in plasma samples of patients with osteoarthritis than in healthy controls. Knockdown of MIR4435-2HG decreased proliferation and promoted cell apoptosis in chondrocytes, while overexpression of MIR4435-2HG enhanced proliferation of chondrocytes and suppressed apoptosis. After treatment with anti-inflammatory drugs (such as naproxen), reducing the joint burden and exercise, the expression level of MIR4435-2HG was increased [14].

Osteoporosis
Guang et al. reported that MIR4435-2HG was down-regulated in plasma of patients suffering osteoporosis compared to healthy controls. They also showed a positive correlation between MIR4435-2HG and bone turnover markers, procollagen-1 N-terminal peptide (PINP) and tartrate-resistant acid phosphatase 5b (TRACP-5b). The phenotype of osteoblasts can be regulated by type I collagen α1/α2 ratio. Knockdown of MIR4435-2HG
suppressed α1 expression but upregulated α2. In contrast, upregulation of MIR4435-2HG elevated α1 but decreased α2. It can be concluded that MIR4435-2HG can affect the phenotype of osteoblasts via alteration in type I collagen α1/α2 ratio [15].

**Osteonecrosis of the femoral head (ONFH)**

Runt-related transcription factor 2 (RUNX2) has been identified as a marker of osteoblastic differentiation [76, 77]. Decreased expression of RUNX2 led to the development of non-traumatic ONFH [78]. The investigation showed that the expression level of MIR4435-2HG in both serum and mesenchymal stem cells (MSCs) samples was significantly downregulated. Silencing and overexpression of MIR4435-2HG in hMSC-BM cells could lead to inhibition and promotion of RUNX2 expression, respectively. To conclude, MIR4435-2HG participates in the progression of non-traumatic ONFH through elevated RUNX2 [13].

**Periodontitis**

Xiaofang et al. demonstrated that the expression level of MIR4435-2HG was elevated in plasma samples of patients with periodontitis compared to healthy controls. They showed that the expression level of MIR4435-2HG was remarkably downregulated after treatment (administration of both oral and topical antibiotics, root planning and scaling). However, after two years of follow-up, the expression of MIR4435-2HG was significantly elevated in patients with recurrence of periodontitis [16].

**Human immunodeficiency virus (HIV) infection**

Expression of MIR4435-2HG is also involved in immune responses against HIV-1 infection. Hartana et al. investigated the expression level of this lncRNA in myeloid dendritic cells (mDCs) obtained from HIV-1 elite controllers (ECs), in whom the virus replication is under control in the absence of antiretroviral treatment, compared to HIV-1-negative healthy controls and those who were treated using antiretroviral therapy. They found that regulatory associated protein of MTOR complex 1 (RPTOR) gene, a major component of the mammalian target of rapamycin (mTOR) signaling pathway, via induction of an epigenetic alteration. Taken together, upregulation of MIR4435-2HG in mDCs from ECs influences immunometabolic activities through different mechanisms, including altered glycolysis, oxidative phosphorylation, epigenetic modifications [79].

**Diagnostic value of MIR4435-2HG**

Several studies have shown that evaluating lncRNAs expression in serum, plasma, and other body fluids may serve as diagnostic or prognostic biomarkers in different disorders that are non-invasive and convenient compared to biopsy and imaging methods. For example, Fu et al. showed the elevated levels of MIR4435-2HG both in tumor tissues and serum samples of gastric cancer patients. They suggested that this lncRNA may be a potential biomarker in gastric cancer [27]. Receiver Operating Characteristic (ROC) Curve Analysis plays a central role in evaluating the diagnostic ability of tests to discriminate the true state of subjects. The diagnostic value of MIR4435-2HG has been evaluated in some tumors and other diseases. MIR4435-2HG can differentiate tumor samples from corresponding controls and distinguish disease status in other non-cancerous conditions. As shown in Table 2, MIR4435-2HG has the best diagnostic power in osteoarthritis subjects.

**Conclusion**

MIR4435-2HG participates in the progression of different human disorders. MIR4435-2HG exerts its functions via the spectrum of different mechanisms, including inhibition of apoptosis, sponging miRNAs, promotion of cell proliferation, increasing cell invasion and migration, and enhancement of EMT. As mentioned above, different miRNAs such as miR-6754-5p, miR-1224-5p, miR-802, and miR-128-3p can be sponged by MIR4435-2HG. On the other hand, MIR4435-2HG can lead to tumor progression by affecting Wnt, TGF-β/SMAD, Nrf2/ HO-1, PI3K/AKT, MAPK/ERK, and FAK/AKT/β-catenin signaling pathways. Several studies have shown that MIR4435-2HG acts as an oncogene in different types of cancer.

The overexpression of MIR4435-2HG in all cancer types that have been studied so far indicates the key role of this lncRNA in cancer progression as an oncogene. Cell proliferation, EMT, invasion, migration, and suppressed apoptosis are key hallmarks of cancer that can be affected by MIR4435-2HG expression. Besides, several studies confirmed the effectiveness of MIR4435-2HG silencing in inhibiting tumor growth in colorectal cancer, esophageal squamous cell carcinoma, gastric cancer, hepatocellular carcinoma, lung cancer, neuroglioma, and prostate cancer.

In contrast, in non-cancerous conditions such as periodontitis, osteoporosis, osteoarthritis, and osteonecrosis of the femoral head, the expression level of MIR4435-2HG has been downregulated. However, in coronary artery diseases, the expression level of MIR4435-2HG was elevated.

The expression level of MIR4435-2HG alters in response to many drugs, including statins (atorvastatin and rosuvastatin), oral and topical antibiotics, anti-inflammatory drugs (such as naproxen) and chemopreventive agent resveratrol. This subject indicates
that MIR4435-2HG has a pivotal function in molecular mechanisms involved in disease development. Therefore, it can be concluded that MIR4435-2HG may serve as a potential therapeutic target for the treatment of various diseases.

Despite fundamental improvement in cancer diagnosis methods, recurrence and metastasis occur in many patients suffering from cancer, therefore, the discovery of new diagnostic biomarkers could be helpful in this regard [80, 81]. Moreover, according to the literature, the diagnostic value of MIR4435-2HG was acceptable in both cancerous and non-cancerous conditions. Detection and measurement of MIR4435-2HG in body fluids such as serum, plasma, and joint fluid suggest that this lncRNA could be used as a non-invasive marker.

Although previous studies have emphasized the role of MIR4435-2HG in the progression of different diseases, few studies has been conducted to describe the possible mechanisms involved in its regulation. Therefore, understanding the mechanisms involved in MIR4435-2HG regulation may shed light on the diagnosis and treatment of several related diseases.

In conclusion, MIR4435-2HG has a pivotal role in cancer progression and critical function in non-neoplastic conditions. Future studies may explain the role of this lncRNA as a potential biomarker and therapeutic target in human disorders, especially in tumors.

### Abbreviations

IncrNA: Long non-coding RNA; miRNAs: MicroRNAs; EMT: Epithelial-mesenchymal transition; MIR4435-2HG: MIR4435-2 Host Gene; YAP1: Yes-related protein 1; NrF2: Nuclear factor erythroid 2-related factor 2; HO-1: Hemeoxygenase-1; GLUT-1: Glucose transporter 1; p-SMAD2: Phosphorylated SMAD2; NTRK3: Tropomyosin receptor kinase C; SOX4: SRY-box transcription factor 4; YBX1: Y-box binding protein 1; SNAIL1: Snail family transcriptional repressor 1; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PRC2: Polycomb repressive complex 2; EZH2: Enhancer of zeste homolog; ChIP: Chromatin immunoprecipitation; p-JNK: Phosphorylated JNK; p-ERK: Phospho-ERK; MAPK: Mitogen-activated protein kinase 1; R3GNT5: UDP-GlcNAc:betaGal beta-1,3-N-acetylg glucosaminyltransferase 5; CDK6: Cyclin dependent kinase 6; TGF-β1: Transforming growth factor β1; CDK14: Cyclin dependent kinase 14; FAK: Focal adhesion kinase; ST8SIA1: ST8 alpha-N-acetyl-neuraminidase alpha-2,8-sialyltransferase 1; mTOR: Mammalian target of rapamycin; TGFBR2: Transforming growth factor-beta receptor type II; TAZ: Tazalizin, phospholipid-lysophospholipid transacetylase; ROCK2: Rho-associated protein kinase 2; MS22: Musashi RNA binding protein 2; IL6: Interleukin like factor 6; cellRNA: Competing endogenous RNA; RBM3: RNA binding motif protein 3; PTEN: Phosphatase and tensing homology; P1NP: Procollagen-1 N-terminal peptide; TRACP-5b: Tartrate-resistant acid phosphatase 5b; RUNX2: Runt-related transcription factor 2; MSDs: Mesenchymal stem cells; HNSCC-bm: Human Mesenchymal Stem Cells-Bone Marrow; RPTOR: Regulatory associated protein of mTOR complex 1; ROC: Receiver operating characteristic; CRC: Colorectal cancer; GC: Gastric cancer; HCC: Hepatocellular carcinoma; NSCLC: Non-small cell lung cancer; OC: Ovarian cancer; BC: Breast cancer; LC: Lung cancer; ccRCC: Clear cell renal cell carcinoma; ESCC: Esophageal squamous cell; PC: Prostate cancer; GBM: Glioblastoma; T-ALL: T-cell acute lymphoblastic leukemia; AML: Acute myeloid leukemia; AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia; AUC: Area under the Curve

### Table 2 Diagnostic value of MIR4435-2HG in cancers and non-cancerous conditions [ALL: Acute lymphoblastic leukemia, AUC: Area under the Curve]

| Disease                  | Expression | Number of samples | Sensitivity | Specificity | AUC  | Sample  | References |
|--------------------------|------------|-------------------|-------------|-------------|------|---------|------------|
| Gastric cancer           | Up         | 51 cancer patients and 53 healthy controls | 90.2        | 74.5        | 88.2 | Plasma  | [26]       |
| Gastric cancer           | Up         | 72 cancer patients and adjacent non-cancerous tissues | 80          | 70          | 83.1 | Serum   | [27]       |
| Hepatocellular cancer    | Up         | 58 cancer patients and 45 healthy controls | 75.9        | 95.9        | 91   | Serum   | [36]       |
| Colorectal cancer        | Up         | 70 cancer patients and adjacent non-cancerous tissues | 72          | 80          | 81   | Tissue  | [21]       |
| Colon cancer             | Up         | 46 cancer patients and 42 healthy controls | –           | –           | 84.8 | Serum   | [20]       |
| Ovarian carcinoma        | Up         | 66 cancer patients and 54 healthy controls | –           | –           | 88.2 | Plasma  | [50]       |
| ALL                      | Up         | 32 cancer patients and 32 healthy controls | –           | –           | 89.5 | Bone marrow | [64]     |
| Renal cell carcinoma     | Up         | 118 cancer patients and adjacent non-cancerous tissues | –           | –           | 94.6 | Tissue  | [67]       |
| Osteoarthritis           | Down       | 78 osteoarthritis and 58 healthy controls | –           | –           | 96   | joint fluid | [14]     |
| Osteoporosis             | Down       | 88 osteoporosis patients and 57 healthy control | –           | –           | 92   | plasma  | [15]       |
| Non-traumatic ONFH       | Down       | 36 ONFH patients and 30 healthy controls | –           | –           | 81.8 | Serum   | [13]       |

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Author details
1 Department of Clinical Biochemistry, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. 2 Department of Biology, Faculty of Science, University of Guilan, Rasht, Iran. 3 Department of Medical Genetics, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. 4 Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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