Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

# Gene Section
## Review

# GLI2 (GLI family zinc finger 2)

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Published in Atlas Database: February 2013

Online updated version : http://AtlasGeneticsOncology.org/Genes/GLI2ID40718ch2q14.html
DOI: 10.4267/2042/51137



## Identity

**Other names:** HPE9, THP1, THP2

**HGNC (Hugo):** GLI2

**Location:** 2q14.2

## DNA/RNA

### Description

The GLI2 gene encodes one of the three zinc finger transcription factors that are involved in Hedgehog signaling. It was identified by using GLI1 cDNA as a probe (Ruppert et. al, 1988). Human GLI2 gene comprises 13 exons (Roessler et al., 2005).

## Protein

### Description

**Protein:** Human GLI2 was originally identified as a Tax-helper protein (THP) that binds to Tax-responsive element in the long terminal repeat of the human T-cell leukemia virus (Tanimura et al., 1998). However, when compared to orthologous GLI2 genes from different species, the human mRNAs lacked a part of the 5' region encoding the evolutionarily conserved N-terminus of GLI2.

Roessler et al discovered a 5' sequence encoding 328 amino acids and showed that this previously undescribed amino-terminal repressor domain was essential for the dominant negative activity of the human GLI2 (Roessler et al., 2005). Thus, the full length GLI2 contains 1586 amino acids and in vitro transcriptional activity of the full length GLI2 is about 30 fold lower than the N-delta GLI2, previously known as GLI2 (Roessler et al., 2005). The predicted molecular weight of the full length GLI2 is 197 kDa.

**GLI2 promoter:** The promoter region of GLI2 has been cloned and defined by Dennler et al. (Dennler et al., 2007). 5'-RACE was used to identify the transcription start site and the promoter sequence was defined to be about 1600-bp upstream of the transcription initiation site (Dennler et al., 2007).

**Binding sequence:** The consensus binding sequence GACCACCCA for the three GLI transcription factors was first described by Kinzler et al. (Kinzler, et al., 1988) and many direct GLI target genes have been identified using the consensus binding sequence. Later, other natural non-consensus sequences have been found to be comparably active in the luciferase reporter assays in response to activated GLI2 expression (Winklmayr et al., 2010).

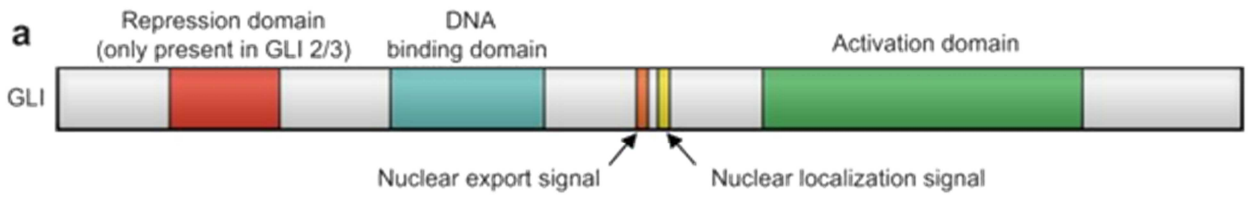


**Figure 1. Schematic representation of GLI functional domains.** (Fernandez-Zapico et al., 2008).

**Structure:** GLI2 belongs to the C2H2 type zinc finger domain protein family. It has a DNA binding domain of five zinc fingers, which are very highly homologous in the three GLIs. The crystal structure revealed by Pavlevich et al. (1993) showed that the fourth and fifth zinc fingers of GLI are responsible for all but one of the protein-DNA base contacts in a conserved nine base-pair region (Pavletich et al., 1993).

GLI2 protein has the repressor domain at N-terminus (Roessler et al., 2005) and activation domain at its C-terminus (Figure1). Unmasking of the strong activation potential of GLI2 through modulation of the N-terminal repression domain is one of the key mechanisms of the Shh signaling (Sasaki et al., 1999).

There is also a processing determinant domain of GLI2 at the C-terminal end of the protein and this domain was found to be the determining factor for the differential processing of the protein by proteasomes (Pan et al., 2007). It is a 197 aa residue between the zinc-finger DNA binding domain and first of 6 Protein Kinase A (PKA) site of GLI2 protein (Li et al., 2011).

In addition to proteolytic processing, alternative splicing may be another important regulatory mechanism for the modulation of repression and activation properties of the GLI2 protein and the generation of protein isoforms with different activities (Speek et al., 2006).

There is also a predicted nuclear export signal and nuclear localization signal domains in the GLI2 protein as depicted in Figure 1.

## Expression

In the integrative genome analysis of GLI2 orthologs, it was found that human GLI2 mRNA was expressed in embryonic stem cells, NT2 cells, fetal lung, fetal heart, regenerating liver, gastric cancer, and other tumors. Mouse GLI2 mRNA was expressed in unfertilized egg, ES cells, and EG cells (Katoh et al., 2008).

## Localisation

In a study tracking the cellular localization of GLI2, it has been described that GLI2 shuttles in and out of cilium and with the activation of HH signaling, the protein localizes to the nucleus from its primary cytoplasmic localization. However, exogenous GLI2 localizes into the cytoplasm (Kim et al., 2009a).

## Function

**Hedgehog signaling mediated functions**

GLI2 is one of the components of Hedgehog signaling and one of the three zinc finger transcription factors involved in this signaling pathway. GLI2 is thought to be the primary transcription activator of HH signaling along with GLI1 and to lesser extent GLI3 (Li et al., 2011). Hedgehog signaling pathway is a well characterized pathway and the role of GLI transcription factors are modeled distinctly in the absence or presence of HH ligands. In the absence of HH ligand, GLI proteins are processed and repressor forms are translocated into the nucleus whereas in the presence of HH ligand with the activation of SMO, the active forms of GLI proteins are translocated to the nucleus where they bind and activate their target gene expression (Javelaud et al., 2012). Processing of GLI2 and GLI3 N-terminus represents a critical mechanism allowing regulation of target genes. GLI2 functions as a primary activator of HH signaling along with GLI1 while GLI3 exhibits weak activity and is considered to function as a repressor.

Due to the lack of repressor domain, GLI1 acts also as an activator where it is a direct target of GLI2 and has been shown to complement some of GLI2 functions in vivo (Dahmane et al., 1997; Ikram et al., 2004; Bai and Joyner, 2001).

There are some other proteins that participate in the transduction of the HH signaling by interacting with GLI proteins. An example is a serine/threonine kinase ULK3 is able to phosphorylate GLI proteins and promote their transcriptional activity but in the absence of HH signaling, ULK3 interacts with the inhibitory protein SUFU promoting GLI2 to its repressor form (Maloverjan et al., 2010). Another such proteins are DYRK, dual-specificity tyrosine-regulated kinases, DYRK2 acts as a scaffold protein for E3 unbiquitin ligase complex and phosphorylates GLI2 for proteasome degradation (Maddika et al., 2009) while DYRK1B inhibits GLI2 activity and promotes GLI3 repressor processing (Lauth et al., 2010).

**Hedgehog signaling independent functions**

GLI2 protein has also been found to be affected by other signaling pathways in hedgehog independent way stressing the importance of this protein. There are increasing evidences that GLI2 expression and activation is regulated by other signaling cascades and molecules.

In a study by Dennler et al. (2007), GLI2 has been shown to be a direct transcriptional target of the TGF-β/SMAD pathway independent from HH receptor signaling, and requires a functional Smad pathway in human normal fibroblasts and keratinocytes and cancer cell lines.

It has also been shown that GLI2 can induce the secretion of IL6 in stromal cells as a model of tumor microenvironment via sonic hedgehog independent signaling cascade and mediate increased immunoglobulin secretion in B-cell malignancies (Elsawa et al., 2011).

In a study on pancreatic cancer cells oncogenic KRAS strongly stimulated GLI function where this effect was ligand independent and occurred downstream of SMO since Cyclopamine treatment did not inhibit the KRAS induced GLI superactivation (Ji et al., 2007).

TGF-β, β-catenin and hyperactive RAS/RAF/MEK/ERK-mediated signaling upregulates GLI2 expression/activity in tumor cells independent of the presence of hedgehog ligand and hyperactivity of these alternate cell signaling pathways is known to occur in many different types of cancer (Jenkins, 2009; Lauth and Toftgard, 2007).

**GLI2 and the tumor microenvironment.**
Metastasizing tumor cells hijack many of the pathways that play major roles during normal development. Many of the embryonic developmental signaling pathways, such as Wnt, Hedgehog (HH), and Notch pathways, affect the survival of tumor stem cells and orchestrate a complex microenvironment that promotes tumor survival and progression (Das et al., 2012). In this context, several studies have addressed a putative role of GLI2 in the tumor microenvironment in mediating the cellular crosstalk in certain cancers.
Evidence of the crosstalk between TGF-beta and HH signaling pathways exists in non-canonical HH signaling pathway which could challenge cancer therapy (Javelaud et al., 2012).
TGF-beta signalling is known to modulate the tumor microenviroment by orchestrating fibroblast chemotaxis and activation of immune cells and stromal-epithelial cross-talk (Stover et al., 2007). TGF-β also induces GLI2 expression in various human cell types, including normal fibroblasts and keratinocytes, as well as various cancer cell lines affecting tumor progression, apoptosis and cell cycle (Javelaud et al., 2011a). To date, the precise role of TGF- β-GLI2 signaling axis in the tumor microenvironment has not been addressed.
One study stressing the role of GLI2 on tumor microenvironment showed that GLI2 can mediate secretion of IL-6 in bone marrow stromal cells via a SHH-independent signaling cascade.
The cytokine CCL5 initiates signaling through the CCR3 receptor leading to activation of the PI3K/AKT signaling pathway ultimately increasing the expression of IL-6. IL-6 in turn leads to increased immunoglobulin secretion by malignant B-cells (Elsawa et al., 2011).
A role for GLI2 in the tumor microenvironment in breast cancer metastasizing to the bone has been described. The production of parathyroid hormone-related peptide (PTHrP), a major factor involved in tumor-induced osteolysis caused by metastatic breast cancers, is driven at least in part by GLI2 both in vitro and in vivo (Sterling et al., 2006).
In B-cell chronic lymphocytic leukemia (B-CLL), it has been demonstrated that inhibiting HH signaling in stroma inhibits bone marrow stromal cell-induced survival of B-CLL cells, suggesting a role for HH signaling in the survival of B-CLL cells evidence supported by gene expression profiling of primary B-CLL cells and disease progression of B-CLL patients with clinical outcome (Hegde et al., 2008).

### *Homology*

GLI2 shares 44 % sequence identity with GLI3 and is structurally more similar to GLI3.

## Mutations

**Note**
Loss-of-function mutations in the human GLI2 gene are associated with a distinctive phenotype whose primary features include defective anterior pituitary formation and pan-hypopituitarism, with or without overt forebrain cleavage abnormalities, and HPE-like mid-facial hypoplasia (Roessler et al., 2003).

## Implicated in

### *Various cancers*

**Note**
GLI2 has been found to be expressed and affect various types of cancer cells and has been a candidate for novel therapeutic applications in the treatment of various cancers.

### *Epidermal cancer*

**Note**
In epidermal malignancies, human GLI2 has been shown to antagonize contact inhibition and epidermal differentiation. Induction of GLI2 oncogene in human keratinocytes activates the transcription of a number of genes involved in cell cycle progression including E2F1, CCND1, CDC2 and CDC45L, while it represses genes associated with epidermal differentiation, suggesting a role for GLI2 in HH-induced epidermal neoplasia by opposing epithelial cell cycle arrest signals and epidermal differentiation (Regl et al., 2004). Basal GLI2 expression in melanoma cells largely depends upon autocrine TGF-β signaling and high levels of GLI2 expression is associated with loss of E-cadherin expression and increased invasive capacities (Alexaki et al., 2009; Javelaud et al., 2011b).

### *Basal cell carcinoma*

**Note**
GLI2 plays a key role in activation of the activin/ Bone Morphogenic Protein (BMP) antagonist FST in response to HH signaling in basal cell carcinoma (BCC). This provides new evidence for a regulatory interaction between HH and activin/BMP signaling in hair follicle development and BCC (Eichberger et al., 2008). GLI2 has also been found to render cells resistant to TRAIL (tumor necrosis factor-related apoptosis-inducing ligand)-mediated cell death in BCC by directly regulating cFlip and Bcl-2 (Kump et al., 2008). Together, these data suggest a
novel therapeutic approach of targeting GLI2 in tumors with dysregulated Hedgehog signaling. Apart from that, it has been demonstrated that GLI2 directly activates GLI1 by binding the GLI-binding consensus sequence in the GLI1 promoter and retrovirally expressed GLI2 induces the expression of endogenous GLI1 in human primary keratinocytes (Ikram et al., 2004). There is also a positive GLI1-GLI2 feedback loop in HH-mediated epidermal cell proliferation (Regl et al., 2002). GLI2 has been shown to be expressed in the interfollicular epidermis and the outer root sheath of hair follicles in normal skin as well as in BCC tumor islands implicating GLI2 in regulating epidermal cell

proliferation and skin tumorigenesis (Ikram et al., 2004).

## Prostate cancer

**Note**

The role of GLI2 in maintaining the tumorigenic properties and growth of prostate cancer cells has been demonstrated suggesting that GLI2 could be a therapeutic target for the treatment of prostate cancer (Thiyagarajan et al., 2007). GLI2 protein is overexpressed in prostate cancer cell lines and primary prostate tumors, whereas the level of GLI2 mRNA is not appreciably different in normal and neoplastic prostate and GLI2 expression has been shown to be regulated by beta-Transducin Repeat Containing Protein 2 (BTrCP2) in HH pathway-associated human prostate cancer (Bhatia et al., 2006).

## Colon cancer

**Note**

Targeting of the smoothened receptor (SMO) using cyclopamine had a minimal effect on colon cancer cell survival in comparison to the inhibition of GLI (using GANT61), which induced extensive cell death in 7/7 human colon carcinoma cell lines suggesting that GLI transcription factors may constitute a molecular switch that determines the balance between cell survival and cell death in human colon carcinoma (Mazumdar et al., 2011a). GANT61 specifically targeted GLI1 and GLI2 substantiated by specific inhibition of (i) direct binding of GLI1 and GLI2 to the promoters of target genes Huntingtin Interacting Protein 1 (HIP1) and BCL-2, (ii) GLI-luciferase activity, and (iii) transcriptional activation of BCL-2. These findings establish that inhibition of HH signaling at the level of the GLI genes is critical in the induction of DNA damage in early S-phase, leading to cell death in human colon carcinoma cells (Mazumdar et al., 2011b).

## Pancreatic cancer

**Note**

In pancreatic cancers, recent evidence from in vitro and in vivo studies suggests that the Sonic Hedgehog (SHH) signaling pathway is aberrantly reactivated and recognized as one of the mediators in the majority of pancreatic cancers (PCs) (Ogden et al., 2004). Therefore, SHH blockade has the potential to prevent disease progression and pancreatic cancer metastases (Yauch et al., 2008). Sustained GLI2 activity has been shown to inhibit cell viability and induce apoptosis in pancreatic cancer cell lines and pancreatic cancer stem cells (CSCs) while activated GLI genes repress death receptors (DRs) and Fas expression, up-regulate the expressions of Bcl-2 and Platelet-derived Growth Factor Receptor alpha precursor (PDGFRα) and facilitate cell survival (Singh et al., 2011). In studies in which an activated version of the GLI2 transcription factor was expressed in β-cells that are also devoid of primary cilia, there was impaired β-cell function and insulin secretion, resulting in glucose intolerance in transgenic mice (Landsman et al., 2011). This phenotype was accompanied by reduced expression of both genes critical for β-cell function and transcription factors associated with their mature phenotype indicating that deregulation of the HH pathway impairs β-cell function by interfering with the mature β-cell differentiation state (Landsman et al., 2011).

## Breast cancer

**Note**

In frequent metastatic breast cancer to the bone where tumor cells receive signals such as Transforming Growth Factor- beta (TGF-β), this results in an upregulation of GLI2 expression and, in turn, increases the secretion of important osteolytic factors such as parathyroid hormone-related protein (PTHrP) (Johnson et al., 2011b). The guanosine nucleotide 6-thioguanine (6-TG) inhibits PTHrP expression and blocks osteolytic bone destruction in mice inoculated with bone metastatic cells though GLI2 signaling. This suggests that the clinical use of 6-TG or other guanosine nucleotides may be a viable therapeutic option in tumor types expressing elevated levels of GLI proteins (Johnson et al., 2011a).

## Liver cancer

**Note**

Aberrant expression of Hedgehog components have been reported in hepatocellular carcinoma (HCC) (Kim et al., 2007). A role for GLI2 has been addressed to predominantly affect HCC susceptibility to TRAIL and cell proliferation (Zhang et al., 2011). Among the expression levels of Hedgehog pathway components, GLI2 levels were higher in human HCC lines compared with normal liver as well as in tumor tissue from HCC patients (Kim et al., 2006).

## B-cell cancers

**Note**

In B-cell malignancies such as Waldenström macroglobulinemia (WM) and others including multiple myeloma (MM) and monoclonal gammopathies of undetermined significance (MGUS), it has been shown that GLI2 can induce the secretion of the proinflammatory cytokine IL-6 in the surrounding stromal cells via PI3K/AKT signaling cascade and mediates increased immunoglobulin secretion by malignant B-cells (Elsawa et al., 2011).

In multiple myeloma, the mitogen-activated protein kinase MEK1 modulates GLI2 both at the mRNA and protein level. Constitutively activated MEK1 prolonged the half-life of GLI2 and increased its nuclear translocation, accompanied by attenuated ubiquitination of GLI2 protein in several MM cells relative to normal B cells (Liu et al., 2009). Moreover, combined treatment with RSK, a protein kinase functioning downstream of MEK-ERK cascade and GLI inhibitors led to an enhanced apoptosis of MM

cells indicating that MEK-RSK cascade positively regulates GLI2 stabilization and represses its degradation via inhibiting Glycogen Synthase Kinase 3 beta (GSK-3β)-dependent phosphorylation and ubiquitination of GLI2 (Liu et al., 2012).
In diffuse large B-cell lymphoma (DLBCL), cancerous cells have been found to express GLI2 along with other sonic hedgehog proteins, providing evidence that dysregulation of the SHH pathway may be involved in the pathogenesis of the disease (Kim et al., 2009b).
In Mantle cell lymphoma (MCL), GLI2 was expressed along with SHH-GLI signaling proteins and perturbation of this signaling in the presence of exogenous SHH/cyclopamine significantly influenced the proliferation of malignant cells (Hegde et al., 2008). Furthermore, down-regulation of GLI transcription not only resulted in significantly decreased proliferation of the MCL cells but also significantly increased their susceptibility to doxorubicin, a standard chemotherapeutic drug used for MCL treatment (Hegde et al., 2008). Down-regulation of GLI 1 and GLI2 decreased cyclin D1 and BCL2 transcripts, suggesting these key molecules might be regulated by GLI proteins in MCL therefore molecular targeting of GLI is a potential therapeutic approach to improve the treatment for MCL patients (Hegde et al., 2008).

### Ovarian cancer

**Note**

In ovarian cancer, targeting Jagged1, the ligand of Notch in tumor cells downregulates GLI2, thereby partly induces apoptosis, reduces cell viability, and reverses taxane-mediated effects in vitro and in vivo (Steg et al., 2011).

### Osteosarcoma

**Note**

GLI2 was found to be overexpressed in human osteosarcoma biopsy specimens and knockdown by RNA interferences prevented osteosarcoma growth and anchorage-independent growth (Nagao et al., 2011).
Also, knockdown of GLI2 promoted the arrest of osteosarcoma cells in G(1) phase and was accompanied by reduced protein expression of the cell cycle accelerators cyclin D1, S-phase associated kinase (SKP2) and phosphorylated Retinoblastoma protein (Rb) but increased the expression of p21(cip1).
In addition, over-expression of GLI2 promoted mesenchymal stem cell proliferation and accelerated their cell cycle progression. Finally, evaluation of mouse xenograft models showed that GLI2 knockdown inhibited the growth of osteosarcoma in nude mice suggesting inhibition of GLI2 as an effective therapeutic approach for patients with osteosarcoma (Nagao et al., 2011).

### GLI2 in stem cells

**Note**

In multipotential neural stem cells (NSCs) in the central nervous system (CNS), expression of the sox2 gene, which is essential for the maintenance of NSCs, is regulated by GLI2 (Takanaga et al., 2009). GLI2 binds to an enhancer that is vital for sox2 expression in telencephalic neuroepithelial (NE) cells, which consist of NSCs and neural precursor cells. Downregulation of GLI2 in NE cells in vitro and in vivo inhibits cell proliferation and the expression of Sox2 and other NSC markers, including Hes1, Hes5, Notch1, CD133, and Bmi1 (Takanaga et al., 2009).
This also induces premature neuronal differentiation in the developing NE cells. In addition, Sox2 expression decreases significantly in the developing neuroepithelium of GLI2-deficient mice revealing a novel transcriptional cascade, involving GLI2→Sox2→Hes5, which maintains the undifferentiated state of telencephalic NE cells (Takanaga et al., 2009).
In embryonic stem cells, important molecules in the development of embryonic heart muscle and enhancers of cardiomyogenesis, GLI2 and myocyte enhancer factor 2C (MEF2C) are able to bind each other's regulatory elements, activate each other's expression and form a protein complex that synergistically activates transcription, enhancing cardiac muscle development (Voronova et al., 2012).
GLI2 overexpression and p53 deficiency has been shown to promote the progression of benign cartilage tumors to malignant state in a mouse model (Ho et al., 2009).

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*This article should be referenced as such:*

Amarsaikhan N, Elsawa SF. GLI2 (GLI family zinc finger 2). Atlas Genet Cytogenet Oncol Haematol. 2013; 17(8):516-522.