Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Review

GRHL2 (grainyhead like transcription factor 2)

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Abstract

A mammalian homolog of Drosophila Grainyhead protein, Grainyhead like 2 belongs to the Grainy Head-Like Proteins/CCAAT binding protein, GRH/CP2 family which is conserved from drosophila to mammals (Venkatesan, 2003). In mammals, there are 3 members of the family, GRHL1-3, the expression of which exhibit differential spatiotemporal expression patterns during development and in adult tissues. The GRHL family members are essential developmental transcription factors in epithelial cell morphogenesis/differentiation and in tumorigenesis (Stramer and Martin, 2005; Werth et al., 2010). Although the family members have common molecular and biological functions during development, they rarely exhibit functional redundancy due to different gene targets (Boglev et al., 2011). GRHL2 can act as a tumor-suppressor or oncogene depending upon tissue of expression.

Keywords
GRHL2; Transcription factor; development, keratinocyte; differentiation; cancer

Identity

Other names
Transcription Factor CP2-Like 3 (TFCP2L3)
Brother Of Mammalian Grainyhead (BOM)
Grainyhead-Like Protein 2 Homolog Deafness Autosomal Dominant 28

HGNC (Hugo)
GRHL2

Location
8q22.3

Location (base pair)
Starts at 101,492,440 and ends at 101,669,726 bp (GRCh38:CM000670.2) ; + strand

Orange arrow indicates the GRHL2 (NC_000008.11) location on chromosome 8 on positive strand shown as black line. Green arrow indicates NCALD, the closest gene to GRHL2.

DNA/RNA

Note

The GRHL2 located on chromosome 8q22.3 is on the forward strand and spans 177287 bp on the

genome. It has 16 exons. The primary mRNA transcript 1 (NM_024915.3) is 5231 bp in length and contains an open reading frame of 1878 bp (NCBI ,2017).

Exons are shown in boxes; lines indicate introns. The encoding exons are in green. The start codon ATG and stop codon TGA are shown.

Description

The human GRHL2 gene is located on chromosome 8 and contains 16 exons.

Transcription

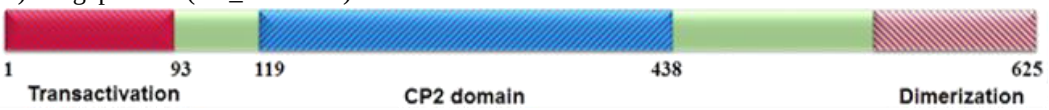
It appears that an internal 5' splicing site within the first exon of GRHL2 generates an alternate GRHL2 mRNA (NM_001330593) with a 203-base deletion containing the first Met encoding AUG codon in its 5'-end. This results in the utilization of the second AUG within exon 2 giving rise to an amino-terminally truncated (16 residues) GRHL2 isoform (NP_001317522.1), GRHL2v (17-625) that displays a disrupted transactivation function.

Protein

Note

GRHL2 variant 1 transcript encodes a 625 amino acids (aa) long protein (NP_079191.2). Based on GHRL2 and its Drosophila homolog GRH, the protein isoform 1 contains transcription activation domain at the amino-terminus (1-93 aa) and a large CP2 Transcription Factor domain between 119-438 aa that is responsible for DNA binding as well as a dimerization domain at the carboxyl-terminus (Attardi and Tijan, 1993, Kokoszynska et al., 2017; Uv, Thompson and Bray, 1994). Resulting from the alternative splicing of GHRL2 transcript, GRHL2 isoform 2 lacks the first 16 amino-acids and is a 609 aa long protein (NP_001317522.1). GRHL2 isoform is reported to counteract the oncogenic potential of GRHL2 isoform 1 by acting as a dominant negative manner (Werner et al., 2013).

Proteomic analyses also suggest that GRHL2 is a phosphoprotein in various normal and cancerous tissues as well as in cell lines (Mertins et al., 2016).



GRHL2, composed of 625 aa, contains a transactivation domain between 1-93 aa; a CP2 domain between 119-438 aa responsible for DNA binding and a dimerization/oligomerization domain at the carboxyl-terminus.

Description

GRHL2 protein is a transcription regulator that has a conserved CP2 domain.

Expression

In human adults, GRHL2 is expressed in the placenta, brain, kidney, prostate, thymus, lung, salivary gland, mammary gland, digestive tract, and pancreas (Wilanowski et al., 2002; Peters et al., 2002).

It is also reported that MIR194 and MIR217 inhibit the cellular proliferation and promote cellular differentiation by targeting the GRHL2 translation (Yu et al., 2017; Zhu et al.,2016).

Localisation

GRHL2 is localized primarily in the nucleus (Chen et al., 2010; Petrof et al., 2014). GRHL2 is also observed to be localized in the cytoplasm and at the inner cell membrane (Petrof et al., 2014).

Function

GRHL2 is a transcription factor. The GRHL2 encodes a 71 kDa protein functions as DNA binding protein that interacts with permutations of the consensus sequence 5'-AACCGGTT-3' (Werner et al., 2013). GRHL2 appears to act as transcription repressor and/or activator depending on chromatin context of target genes (Mehrazarin.et al., 2015).

Observations with experimental animal models indicate that the knock-out of, or nonsense mutations in, the mouse Grhl2 gene results in embryonic lethality due to defects in neural tube closure, epithelial morphogenesis, and barrier formation by de-regulation of cell junction protein expressions (Werth et al.,2010; Pyrgaki, Liu and Niswander, 2011). This finding emphasizes the essentiality of Grhl2 for epithelial and neural morphogenesis during embryogenesis.

GRHL2 is also implicated in the carcinogenesis of various tissues and organs. Consistent with its role in epithelial morphogenesis, GRHL2 is shown act as tumor-suppressor by controlling the epithelial-

mesenchymal transition (EMT), an essential characteristic of tumor progression (Wellner et al., 2009). In contrast, GRHL2 is also reported to act as an oncogene by promoting cell proliferation and survival (Cieply et al., 2013). Although underlying reasons are yet unclear, de-regulation of tissue/organ specific expression of the GHRL2 gene together with tissue/organ specific gene targets of GHRL2 is suggested to underlie the dual effects of GRHL2 on carcinogenesis (Wellner et al., 2009).

Homology

GRHL2 is a conserved gene among vertebrates and in Drosophila.

Mutations

Note

Tyr to His substitution at the position 398 and Ile to Lys at 498 of GHRL2 are observed in ectodermal dysplasia (Petrof et al., 2014). In addition, single nucleotide insertion at the position 1609 is reported to lead to frame shift and early stop codon in the encoding transcript (Peters et al., 2002).

Germinal

Haploinsufficiency for GRHL2 implicated in non-syndromic sensorineural deafness- autosomal dominant type 28 (DFNA28), due to frameshift mutations and single nucleotide polymorphism in the gene (Van Laer et al., 2007), are associated with hearing loss. (Peters et al., 2002). These variations in the GRHL2 gene are suggested to likely result in deregulated gene expressions encoding for cell junction proteins and ion channels in the otic epithelial cells, which are important for the inner ear development and homeostasis (Han et al., 2011).

It is also reported that mutations in the GRHL2 sequences encoding DNA binding domain result in an autosomal-recessive ectodermal Dysplasia syndrome (Petrof et al., 2014).

Implicated in

Breast cancer

GRHL2 is implicated to play a role in epithelial-mesenchymal transition (EMT) of breast cancer. It appears that increased expression of GHRL2 is inversely correlated with increased tumor stages and the presence of lymph node metastases (Cieply et al., 2012). Extending these observations, experimental studies using breast cancer cell models further suggest that the expression of GRHL2 is downregulated specifically in the claudin-low subclass breast tumors and in basal-B subclass breast cancer cell lines, where it suppresses EMT, enhances anoikis sensitivity, and suppresses mammosphere generation. Moreover, it appears that the GRHL2 expression prevents tumor initiation in xenograft animal models and suppresses the emergence of phenotype indicative of cancer stem cell (Cieply et al.,2012).

Esophageal cancer

Studies suggest that de-regulated expression of the GRHL2 gene is common in esophageal cancer. The expression of GRHL2 is observed to be higher in esophageal tumor tissue than that of in adjacent tissues (Shao et al., 2017). The level of GRHL2 expression appears also to be associated with tumor differentiation and to show correlation with lymph node metastasis and invasion depth.

Gastric cancer

GRHL2 is suggested to be a tumor suppressor in gastric tissue. The GRHL2 expression and GRHL2 synthesis is reported to be reduced in gastric cancer compared to normal gastric tissues; it is therefore suggested that the down regulation of the GRHL2 expression contributes tumor invasion and metastasis (Xiang et al., 2008). Consistent with this, the GRHL2 overexpression appears to inhibit the invasion and migration of cell models derived from gastric cancer (Xiang et al., 2017).

Prostate cancer

Based on gene expressions analyses, the GRHL2 expression is observed to be upregulated in prostate cancer (Paltoglou et al., 2017; Danila et al., 2014).

Kidney cancer

Based on publically available data sets of 593 clear cell renal cell carcinoma (ccRCC) and 389 normal kidney samples and verification with patient samples, GRHL2 is found to be downregulated in tumor cells compared normal tissue. Moreover, GRHL2 expression observed to be associated with higher chances for disease relapse (Butz et al,. 2014). Extending these observations on tumor-repressor properties of GRHL2, experimental studies showed that silencing of GRHL2 expression in a non-tumorigenic kidney cell line results in an increased cell proliferation and increased resistance to apoptosis (Pawlak et al., 2017).

Ovarian cancer

The overexpressed GRHL2, due to hypomethylation, is observed to be significantly higher in low malignant potential (LMP) and high-grade (HG) serous epithelial ovarian cancer (EOC) tumors compared with normal tissue. Cell lines modelling EOC display an invasive and metastatic phenotype (Faddaoui et al., 2017). The oncogenic potential of GRHL2 is further suggested by the observations that the suppression of GRHL2 inhibits the proliferation, migration and invasion in ovarian cancer cell models (Chung et al., 2016).

Colorectal cancer

The expression of the GRHL2 is reported to be upregulated in colorectal cancer (CRC) samples compared to control non-tumorigenic tissue assessed

with immunohistochemistry, qRT-PCR, and western blot analyses. It appears that elevated levels of the GRHL2 expression are associated with tumor progression due to higher levels of cell proliferation. Consistent with these observations, the repression of GRHL2 synthesis decreases the proliferation by inhibiting cell cycle progression of CRC cell models and impairs tumor growth in a xenograft mouse model (Quan et al., 2014).

Cervical cancer

Analyses of cervical lesions of cancer patients indicate that the GRHL2 expression is diminished at both mRNA and protein level compared with normal tissue, which is also consistent with the expression analyses of cell lines derived from cervical cancer (Reyes et al., 2014).

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