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Gene Section
Review

EHMT2 (euchromatic histone-lysine N-methyltransferase 2)

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Abstract: Review on EHMT2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: BAT8, C6orf30, G9A, GAT8, KMT1C, NG36

HGNC (Hugo): EHMT2

Location: 6p21.33

Local order: HSPA1A - HSPA1B - NEU1 - SLC44A4 - **EHMT2** - C2 - ZBTB12.

DNA/RNA

Description

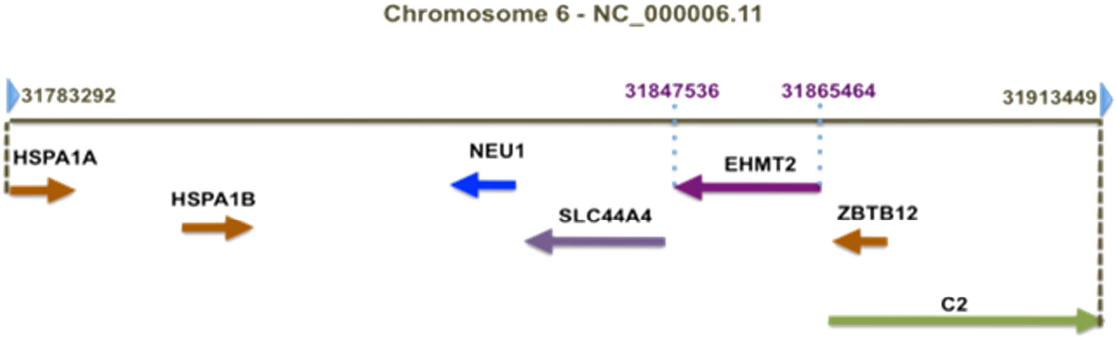
The human EHMT2/G9a Gene (NC_000006.11) is located on the minus strand and spans 17929 bps of genomic region (31847536 - 31865464). The long isoform of EHMT2/G9a comprises 28 exons, whereas the short isoform consists of 27 exons and lacks the sequence corresponding to exon 10 of the long isoform.

Transcription

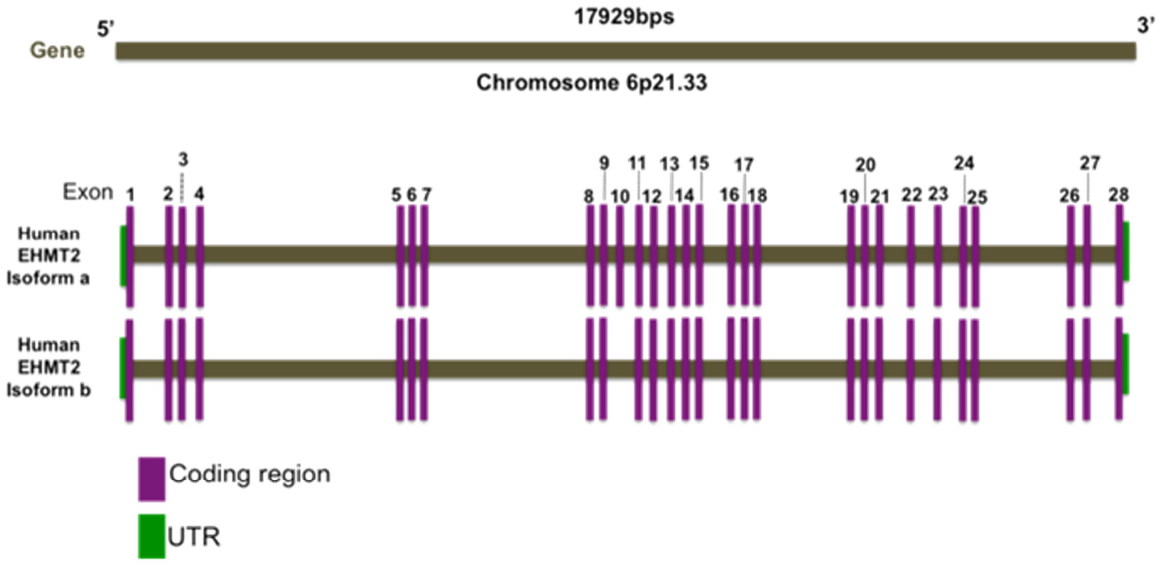
EHMT2/G9a gene has two differentially spliced transcript variants (Brown et al., 2001). G9a transcript variant I NG36/EHMT2 (accession number NM_006709.3) also called long isoform or isoform a, has 3982 bps open reading frame. G9a transcript variant II NG36/EHMT2-SP1 (accession number NM_025256.5) also called short Isoform or isoform b, has open reading frame of 3880 bps (Brown et al., 2001).

Pseudogene

There is no known pseudogene for EHMT2/G9a.



Genomic location of EHMT2/G9a gene along with adjustment genes on chromosome 6 (minus strand).



EHMT2/G9a gene and RNA structure. Schematic representation of the human EHMT2/G9a gene organization demonstrating the relative position of each of the 28 exons (5'UTR, exons and 3'UTR are not drawn to scale). The shorter EHMT2 isoform b has missing exon 10 compared to full length EHMT2.

Protein

Description

EHMT2/G9a isoform a (accession number NP_006700.3) is composed of 1210 amino acid residues while the shorter isoform b (accession number NP_079532.5) comprises 1176 amino acid residues (Figure 2). The G9a protein contains several evolutionarily conserved domains including, the N-terminus transcription activation domain (TAD), E-rich domain containing 24 contiguous glutamic acid residues and the cysteine (Cys) rich domain that contains 12 cysteine residues, the centrally located ankyrin (ANK) domain containing seven ankyrin repeats and the C-terminus SET domain (Milner and Campbell, 1993; Brown et al., 2001; Dillon et al., 2005). Functionally, the TAD domain of G9a has been shown to be involved in transcription activation and is sufficient to activate transcription of several nuclear receptor genes (Lee et al., 2006; Purcell et al., 2011, Bittencourt et al., 2012).

The E-rich domain has been shown to be present in several proteins including the nuclear protein nucleolin, the chromosomal protein HMG1 and the centromere auto-antigen CENP-B (Milner and Campbell, 1993; Brown et al., 2001).

The Cys rich domain acts as a binding site for neuron-restrictive silencing factor (NRSF) and has been shown to be involved in repression of neuronal genes in non-neuronal tissue (Roopra et al., 2004).

The ANK domain, which is conserved in diverse proteins including transcription factors has been shown to be involved in protein-protein interactions (Milner and Campbell, 1993; Sedgwick and Smerdon, 1999), and binding to histone mono- and dimethylated H3 lysine 9 marks (Collins et al., 2008). The C-terminal SET domain is responsible for the methyltransferase activity of G9a (Tachibana et al., 2001; Tachibana et al., 2002) and is also required for interaction with GLP (Tachibana et al., 2005).

Expression

EHMT2/G9a RNA is present in a wide range of human tissues and cells with high levels in fetal liver, thymus, lymph node, spleen and peripheral blood leukocytes and lower level in bone marrow (Milner and Campbell, 1993; Brown et al., 2001).

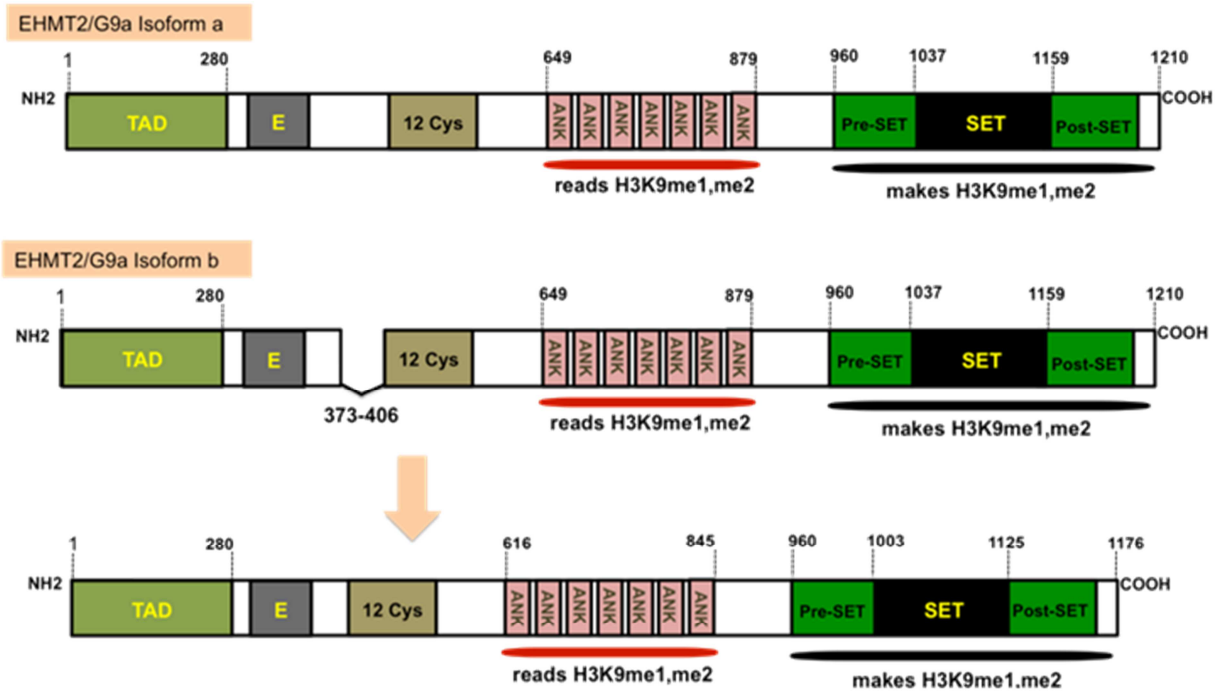
Localisation

EHMT2/G9a is localized in the nucleus. It is mostly associated with euchromatic regions of chromatin and absent from heterochromatin (Tachibana et al., 2002).

Function

The histone methyltransferase G9a mono and dimethylates 'Lys-9' of histone H3 specifically in euchromatin (Tachibana et al., 2001; Tachibana et al., 2002). Furthermore, G9a can also mono and dimethylates 'Lys-27' of histone H3 and mono methylates histone H1 (Tachibana et al., 2001; Chaturvedi et al., 2009; Trojer et al 2009; Weiss et al., 2010; Wu et al., 2011).

In addition, G9a methylates several non-histone proteins including p53, CDYL, WIZ, CSB, ACINUS, DNMT1, HDAC1, KLF12, MyoD, DNMT3a and MTA1 (Rathert et al., 2008; Haung et al., 2010; Chang et al., 2011; Ling at al., 2012; Nair et al., 2013) and automethylates (Chin et al., 2007; Rathert et al., 2008). G9a also plays an important role in mediating DNA methylation through its association with DNA methyltransferases (Epsztejn-Litman et al., 2008; Tachibana et al., 2008; Dong et al., 2008).



Schematic representation of the domain structure of EHMT2/G9a isoform a and isoform b. Isoform b is missing amino acid sequence 373-406 (34 aa) compared to the canonical isoform a (aa 1-1210). Isoform b is numbered according to isoform a, as well as separately. The positions of known domains within G9a are displayed. Transcription activation domain (TAD), E rich, glutamine-rich domain, NRSF- binding cysteine rich domain (12Cys) and ankyrin domain with seven ankyrin repeats and Set domain containing pre and post SET domains.

Transcriptionally, G9a can function both as a corepressor and/or a coactivator of gene expression, (Collins and Cheng, 2010; Yoichi and Tachibana, 2011; Shnakar et al., 2013; Lee et al., 2006; Chaturvedi et al., 2009; Purcell et al., 2011; Chaturvedi et al., 2012; Bittencourt et al., 2012). The corepressor function of the G9a is dependent on its enzymatic activity as well as on its interaction with other factors that are involved in gene repression (Tachibana et al., 2002; Yoichi and Tachibana, 2011; Chaturvedi et al., 2012; Shnakar et al., 2013). G9a gets targeted to specific genes by associating with various transcriptional repressors and corepressors such as, CDP/Cut, E2F6, Gfi1/zfp163, Blimp-1/PRDI-BF1, REST/NRSF, ZNF217 and PRISM/PRDM6 and several others (Tachibana et al., 2002; Ogawa et al., 2002; Gyory et al., 2004; Nashio and Walsh, 2004; Roopra et al., 2004; Daun et al., 2005; Davis et al., 2006; Nagano et al., 2008; Banck et al., 2009; Yoichi and Tachibana, 2011; Shnakar et al., 2013). The coactivator function of the G9a does not require its enzymatic activity but requires association with other transcriptional activators and/or coactivators factors including CARM1, p300, RNA polymerases or the Mediator complex (Lee et al., 2006; Chaturvedi et al., 2009; Purcell et al., 2011; Bittencourt et al., 2012; Chaturvedi et al., 2012).

Functionally, G9a has been shown to play important roles in regulating the expression of genes involved in various developmental and differentiation processes. G9a is indispensible for early embryonic development (Tachibana et al., 2002; Yoichi and Tachibana, 2011). The G9a knockout embryonic stem cells (ESCs) show severe defects in differentiation, suggesting that G9a positively regulates ESCs differentiation (Tachibana et al., 2002; Feldman et al., 2006; Kubicek et al., 2007; Shi et al., 2008). Similarly, G9a is required for proper differentiation, survival and lineage commitment of adult or somatic stem cells i.e hematopoietic progenitor stem cells, retinal progenitor cells (Chen et al., 2012; Katoh et al., 1212). Genome wide studies have revealed the presence of G9a mediated large H3K9 dimethylation (H3K9me2) chromatin blocks (LOCKS) on large chromatin region in the genome (Wen et al., 2009; Chen et al., 2012). These G9a mediated LOCKS are necessary for proper differentiation as the loss of LOCKs inhibits or delays differentiation and lineage commitment of both embryonic and adult stem cells (Wen et al., 2009; Chen et al., 2012). In contrast to its positive regulatory role in maintaining differentiation, G9a has been shown to negatively regulate differentiation by repressing differentiation specific genes in myogenesis and adipogenesis (Shankar et al., 2013; Ling et al., 2012a; Ling et al., 2012b; Wang and Abete-Shen, 2011; Wang et al., 2013).

Furthermore, G9a has been shown to regulate gene expression in multiple other biological processes including, genomic imprinting (Nagano et al., 2008; Wagschal et al., 2008), germ cells development (Tachibana et al., 2007), erythropoiesis (Chaturvedi et

al., 2009; Chaturvedi et al., 2012), T and B cell mediated immune response (Thomas et al., 2008; Lehnertz et al., 2010) and nuclear receptor mediated gene expression (Lee et al., 2006; Purcell et al., 2011; Bittencourt et al., 2012).
In the brain, G9a is required for proper expression of genes involved in lineage specific expression (Roopra et al., 2004, Schaefer et al., 2009), memory consolidation (Gupta et al., 2012), and cocaine induced neuronal responses and behavioural plasticity (Maze et al., 2010).
G9a has been also shown to plays critical role in cell proliferation (Yang et al., 2012), senescence (Takahashi et al., 2012), DNA replication (Esteva et al., 2006; Yu et al., 2012), and in the establishment of proviral gene silencing (Leung et al., 2011).

Homology

EHMT2/G9a homologues have been found in various species like chimpanzee (99.7 % homology), cow (98.1% homology), rat (95.97% homology), C. elegans (25 % homology) and mouse (95.5% homology).

Mutations

Germinal

No mutations have been reported so far.

Somatic

No mutations have been reported so far.

Implicated in

Various cancers

Note

EHMT2/G9a is overexpressed in various types of tumors, which include solid and haematological tumors (Cho et al., 2011). High-level expression of G9a in cancerous cells has been correlated with aggressiveness and poor prognosis in patients of lung, hepatocellular, ovarian, colon cancer and B cell chronic lymphocytic leukemia (Haung et al., 2010).
Functionally, G9a has been linked to multiple cellular functions associated with tumor progression including proliferation, adhesion, migration, invasion, and cancer stem cell maintenance.
Knockdown of G9a protein in cancer cells induces apoptosis suggesting that G9a plays a crucial role in cell cycle regulation of cancerous cells (Watanabe et al., 2008).
Use of G9a-specific inhibitors, had been shown to significantly suppress the growth of cancerous cells, indicating that G9a enzymatic activity plays an important role in cancer development and growth (Cho et al., 2011).
The following paragraphs summarize the discoveries on the functional role of G9a in various types of cancer development.

Lung cancer

Note

Lung cancer is a disease characterized by uncontrolled cell growth of lung tissue. G9a is highly expressed in aggressive lung cancer cells, and its elevated level has been correlated to poor prognosis with increase in cell migration, invasion and metastasis (Chen et al., 2010).
G9a enhances the metastasis of lung cancer cells by repressing expression of the cell adhesion molecule Ep-CAM. High level of G9a in lung cancer cells promotes enrichment of DNA methylation and H3K9 dimethylation marks on Ep-CAM gene promoter region, leading to repression of this gene (Chen et al., 2010).
Depletion of the G9a protein in lung cancer cells reduces the levels of H3K9 dimethylation and decreases recruitment of the transcriptional cofactors HP1, DNMT1, and HDAC1 to the Ep-CAM promoter, leading to de-repression of Ep-CAM gene and inhibition of cell migration and invasion (Chen et al., 2010).

Breast cancer

Note

Human breast cancer is a heterogeneous disease with respect to molecular alterations, incidence, survival, and response to therapy. Claudin-low breast cancer (CLBC) is characterized by the expression of markers of epithelial-mesenchymal transition (EMT), which has been linked with CLBC metastasis (Dong et al., 2012).
G9a promotes EMT expression by repressing E-cadherin expression in CLBC models. G9a associates with Snail and recruits HP1 and DNA methyltransferases to the E-cadherin gene promoter for repression (Dong et al., 2012).
Knockdown of G9a in CLBC models restores E-cadherin expression by suppressing H3K9me2 and DNA methylation, which results in inhibition of cell migration, invasion, suppression of tumor growth and metastasis (Dong et al., 2012).

Prostate cancer

Note

Prostate cancer is one of the most frequent cancers in men. G9a is coexpressed at high levels with Runx2, in metastatic prostate cancer cells and directly regulates the expression of several Runx2 target genes, which are important regulators of tumor growth, invasion and/or metastasis (Purcell at al., 2012).
Downregulation of G9a in prostate cancer cells represses several RUNX2 target genes including, MMP9, CSF2, SDF1, CST7 and enhances the expression of others, such as MMP13 and PIP (Purcell et al., 2012). A study by Kondo et al., (2008) demonstrates that downregulation of G9a in prostate cancer cells, disrupts centrosome and chromosome stability, leading to inhibition of cancer cell growth.

Another study by Yuan et al., (2012) demonstrates that treatment of pancreatic cancer cells with G9a inhibitor BRD4770 induces senescence and inhibits proliferation. Collectively, these studies reveal a potential oncogenic role of G9a in prostate cancer progression.

Gastric cancer

Note

G9a is involved in gastric cancer progression by inhibiting expression of the tumor suppressor gene RUNX3. In RUNX3 expressing gastric cell lines, hypoxia leads to upregulation of G9a, leading to the accumulation of H3K9me2 marks on RUNX3 promoter and repression of RUNX3 expression (Lee et al., 2009). Knocking down G9a in hypoxia-induced gastric cancer cells restores the expression of RUNX3 with suppression of gastric cancer progression (Lee et al., 2009).

Bladder carcinomas

Note

G9a expression is upregulated in human bladder carcinomas compared to non-neoplastic bladder tissues (Cho et al., 2011).

Enhanced expression of G9a promotes the proliferation of bladder carcinomas cells by negatively regulating the tumor suppressor gene SIAH1 (Cho et al., 2011).

G9a suppresses transcription of the SIAH1 gene by binding to its promoter followed by methylation of lysine 9 of histone H3.

Downregulation of G9a activity by knock down or through the use of a G9a specific inhibitor, BIX-01294, significantly suppresses the growth of cancer cells by de-repressing the SIAH1 gene (Cho et al., 2011).

Neuroendocrine tumors

Note

Neuroendocrine tumors (NETs) are neoplasms that arise from cells of the endocrine and nervous systems. A study by Kim et al., (2013) has revealed altered expression of Wnt/β-catenin signaling components in neuroendocrine tumors.

G9a contributes to the pathogenesis and growth of NETs by upregulating the expression of β-catenin. High level expression of G9a in neuroendocrine tumors downregulates the expression of specific β-catenin inhibitory genes inclusing DKK-1, DKK-2, and WIF-1, leading to overexpression of β-catenin, which in turn leads to increased cell proliferation and tumor growth (Kim et al., 2013).

Use of the G9a inhibitor UNC0638 derepresses β-catenin inhibitory genes and suppresses Wnt/β-catenin induced cell proliferation, colony formation and tumor growth, demonstrating the oncogenic potential of G9a in NETs progression (Kim et al., 2013).

Haematological malignancies

Note

G9a is over expressed in haematological malignancies including AML and CML (Haung et al., 2010; Cho et al., 2011).

The oncoprotein EVI-1 (ecotropic viral integration site-1) is aberrantly expressed in myeloid leukemias and has been linked to a poor patient survival rate. A study by Goyama et al., (2010) demonstrates that G9a interacts EVI-1 and contributes to EVI-1-mediated leukemogenesis.

Depletion of G9a protein in EVI-1-expressing progenitors significantly reduces their colony-forming activity, indicating a possible role of G9a in generating leukemia-initiating cells by Evi-1 (Goyama et al., 2010).

JAK2 (Janus kinase 2) mediated phosphorylation plays a critical role during normal hematopoiesis and leukemogenesis.

JAK2 induces leukemogenesis by activating the lmo2 leukemogenic gene through phosphorylation of histone H3Y41 and exclusion of HP1α from chromatin (Dawson et al., 2009).

A recent study by Son et al., (2012) demonstrated that G9a negatively regulates the expression of JAK2 and favors ATRA-mediated leukemia cell differentiation. G9a mediated repression of JAK2, results in the downregulation of H3Y41 phosphorylation on the leukemogenic oncogene lmo2 promoter, indicating a role for G9a in JAK2-H3Y41P-HP1α transcriptional signaling during leukemogenesis (Son et al., 2012).

Breakpoints

Note

No variables are reported for EHMT2/G9a gene so far.

To be noted

Note

In summary, dysregulation of EHMT2/G9a is emerging as an important player in the pathobiology of various forms of cancer suggesting that G9a could serve as a promising therapeutic target for future treatments notably through the use of specific chemical inhibitors.

For example, BIX-01294; a specific inhibitor of G9a methyltransferase activity has been shown to effectively suppress the growth of cancer cells (Cho et al., 2011).

Another G9a inhibitor, BRD4770 induces senescence and inhibits proliferation of cancer cells (Yuan et al., 2012). Finally, a third G9a inhibitor UNC0638 showed similar results as BIX-01294 and BRD4770 and inhibits cell proliferation, colony formation and tumor growth (Kim et al., 2013).

It will be interesting to test the effectiveness of these inhibitors in vivo. Further studies are required for better understanding of the molecular mechanism of G9a mediated positive and negative gene regulatory role in cancer development and for developing efficient therapy.

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