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Gene Section
Review

DNMT3A (DNA (cytosine-5-)-methyltransferase 3 alpha

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Identity

Other names: DNMT3A2, M.HsaIIIA
HGNC (Hugo): DNMT3A
Location: 2p23.3
Local order: The human DNMT3A is telomeric to DTNB (dystrobrevin, beta) and centromeric to POMC (proopiomelanocortin).

Note

DNA methylation occurs mainly in the cytosine residues at the C5 positions of CpG dinucleotides and is important in regulating gene expression, parental imprinting, and maintenance of the genome integrity in mammalian cells (Chen and Li, 2006). Aberrant DNA methylation has been reported to play a vital role in the pathogenesis of acute myeloid leukemia (AML) (Rosenbauer and Tenen, 2007).

In addition, differences in global DNA methylation signatures have been reported to be associated with differences in treatment outcome for patients with AML (Figueroa et al., 2010a; Figueroa et al., 2010b; Melnick, 2010).

Genome-wide DNA methylation patterns are established and maintained by the coordination of DNMT1 and DNMT3 families of DNA methyltransferases. DNMT1 carries out most of the maintenance methylation following DNA replication, whereas DNMT3A and DNMT3B are responsible for de novo methylation during mammalian development (Brenner and Fuks, 2006; Hermann et al., 2004). Recent studies showed that Dnmt1 is required for hematopoietic stem cell proliferation and myeloid/lymphoid differentiation (Trowbridge et al., 2009).

In contrast, conditional deletion of Dnmt3a and Dnmt3b in mouse hematopoietic stem cells impaired self- renewal but not lineage determination, indicating the role of de novo DNA methyltransferase for self-renewal in hematopoietic stem cells (Tadokoro et al., 2007).

The third member of the DNMT3 family is DNMT3L which does not have enzymatic activity due to the lack of some critical catalytic motifs (Brenner and Fuks, 2006).

It regulates the catalytic activity of DNMT3A and 3B (Hata et al., 2002; Suetake et al., 2004).

DNA/RNA

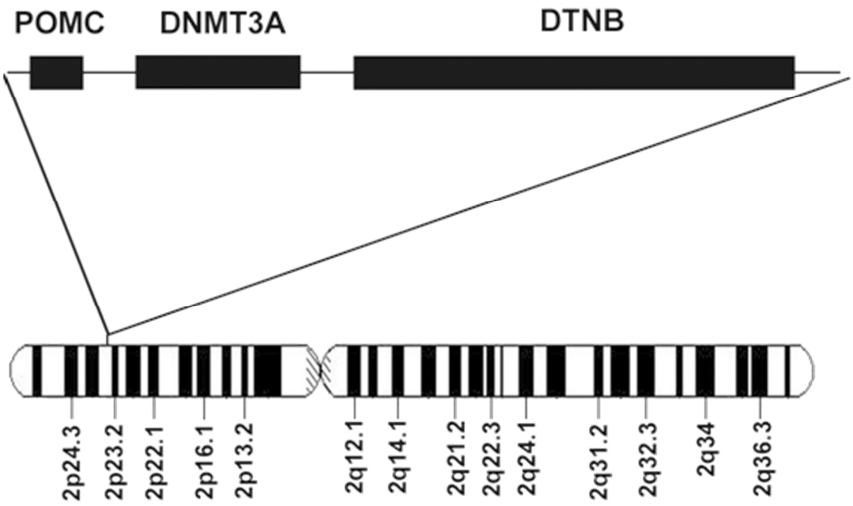
Description

The DNMT3A gene structure is composed of 23 exons (Xie et al., 1999).

A short isoform, named DNMT3A2, is produced from a downstream intronic promoter (Chen et al., 2002).

Transcription

Transcription of DNMT3A is initiated from the downstream intronic promoter and leads to expression of DNMT3A2, an isoform lacking the N-terminal region, in embryonic stem cells (ESCs). Expression of this shorter isoform gradually decreases upon ESC differentiation and switches to the full length DNMT3A which remains expressed at low level in most somatic tissues (Chedin, 2011; Chen et al., 2002).



Genomic localization of human DNMT3A gene. POMC, proopiomelanocortin; DTNB, dystrobrevin, beta.

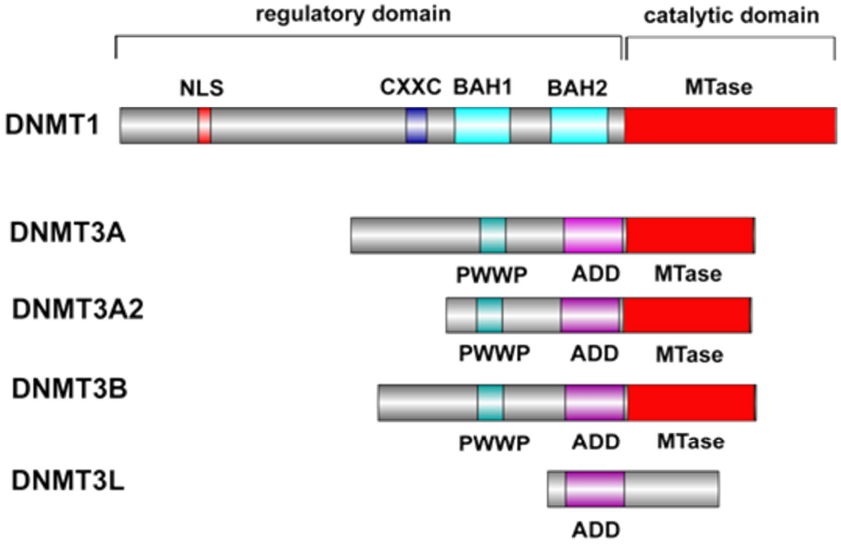
Protein

Description

DNMT3A
AA: 912. EC number: 2.1.1.37. Estimated molecular weight: 101858 Dt.
DNMT3A2
AA: 689. Estimated molecular weight: 77817 Dt.
DNMT3A contains 3 main structure domains: a proline-tryptophan-tryptophan-proline (PWWP) domain, an ATRX, DNMT3, and DNMT3L-type zinc finger (ADD) domain, and the methyltransferase (Mtase) domain. The PWWP domain is responsible for targeting the enzyme to nucleic acid (Chen et al., 2004). In addition, the PWWP domain is also essential for targeting this enzyme to pericentric heterochromatin (Chen et al., 2004; Ge et al., 2004). The ADD domain mediates protein-protein interactions with transcription factors Myc, RP58, the heterochromatin protein HP1, histone deacetylases, and the histone methyltransferase Suv39h1 (Chen and Li, 2006). The Mtase domain contains six highly conserved cytosine C5-DNA methyltransferase motifs (Jurkowska et al., 2011).

Expression

In mouse, Dnmt3a was detected in all tissues except for small intestines, whereas Dnmt3a2 expression was more restricted in testis, spleen and thymus (Chen et al., 2002).
In addition to normal tissues, overexpression of DNMT3A has been reported in various human cancers, such as prostate, pancreatic, gastric, liver cancers (Gravina et al., 2013; Oh et al., 2007; Yang et al., 2011; Zhang et al., 2012). Additionally, DNMT3A were detected substantially overexpressed in certain types of leukemia (Mizuno et al., 2001).



Structure of DNA methyltransferases. NLS, nuclear localization signal; CXXC, a cysteine rich region; BAH, a bromo-adjacent homology domain; PWWP, a proline-tryptophan-tryptophan-proline domain; ADD, an ATRX-DNMT3-DNMT3L-type zinc finger domain; Mtase, a methyltransferase domain.

Localisation

Dnmt3a localizes in the nuclei and is concentrated in nuclear foci.
In contrast, Dnmt3a2 showed a diffused pattern excluding nucleoli and heterochromatin.
In general, Dnmt3a is thought to associate with heterochmatin, whereas Dnmt3a2 associates mainly with euchromatin (Chen et al., 2002).

Function

Similarly to Dnmt1, the Dnmt3a enzyme also uses S-adenosyl methionine (SAM) as the methyl group donor being transferred to the carbon 5 position of the cytosine ring in CpG dinucleotide in DNA.
It is essential for the establishment of DNA methylation patterns during development (Jurkowska et al., 2011).
In addition to the enzymatic function, Dnmt3a was also shown to suppress transcription, independent of its catalytic activity, that was mediated through the interaction with the histone deacetylase and other co-repressors, such as Mbd3 and Brg1 (Datta et al., 2005; Fuks et al., 2001).
Sumoylation of DNMT3A has been reported in the N-terminal domain of the enzyme, which disrupts its interaction with histone deacetylases (HDACs) and thereby impairs the repressive capability of this protein (Ling et al., 2004).

Homology

Dnmt3 family proteins share some structural similarity with Dnmt1 at c-terminal Mtase domain. In addition, the DNMT3A and DNMT3B proteins also contain a conserved cystein-rich ATRX, DNMT3, and DNMT3L-type zinc finger (ADD) domain and the proline-tryptophan-tryptophan-proline (PWWP) domain.
The N-terminal domains of Dnmt3a and Dnmt3b do not share any sequence homology (Chedin, 2011).

Mutations

Somatic

Recurrent DNMT3A gene mutations were recently reported in acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), T-cell lymphoma, and T-cell acute lymphoblastic leukemia (ALL) (Couronne et al., 2012; Grossmann et al., 2013; Hou et al., 2012; Ley et al., 2010; Stegelmann et al., 2011; Walter et al., 2011). The most frequently mutated site is the Arg 882 (R882) residue located in the catalytic domain. These R882 mutants were reported to reduce DNA methylation activity of DNMT3A (Yan et al., 2011).

Implicated in

Acute myeloid leukemia (AML)

Note

DNMT3A mutations frequently detected in 7-29% of AML patients. This mutation was associated with normal karyotype, older age, French-American-British (FAB) M4/M5 subtypes, and poor prognosis.
Multivariate analysis demonstrated that the DNMT3A mutation was an independent poor prognostic factor for over-all survival and relapse-free survival (Hou et al., 2012; Ley et al., 2010; Thol et al., 2011a; Yan et al., 2011).
This mutation was also reported in 35.1% of secondary AML and 16.4% of therapy-related AML in a study of a cohort of 98 patients and found that this mutation was associated with normal karyotype and IDH1/IDH2 mutations, but that it does not affect survival (Shih et al., 2013).
Recent reports further demonstrated that the frequency of DNMT3A mutations is rare in childhood AML and MDS, suggesting that the frequency of DNMT3A gene mutation depends on age (Ho et al., 2011; Thol et al., 2011b).
In addition, it was also reported that AML patients whose leukemic blasts have low DNMT3A activity, either due to loss-of-functions or low gene expression, may benefit from treatment with hypomethylating agents (Metzeler et al., 2012).

Myelodysplastic syndrome (MDS)

Note

Mutations of the DNMT3A gene were detected in 6% of MDS patients and amino acid R882 was the most common mutation site.
Patients with DNMT3A mutations had worse overall survival compared with patients without these mutations and more rapid progression to AML (Walter et al., 2011).

Myeloproliferative neoplasms (MPN)

Note

In a study of a cohort of 155 patients with MPN, an overall frequency of 10% mutations were most frequently detected in secondary AML (sAML: 17%) and myelofibrosis (MF: 15%), followed by polycythemia vera (PV: 7%) and essential thrombocythemia (ET: 3%).
These alterations occurred concurrently with JAK2, IDH1/2 and ASXL1 mutations.
In addition, these mutations are associated with more advanced stages of MPNs and with an overall poor prognosis (Stegelmann et al., 2011).

T-cell lymphoma

Note

DNMT3A mutations were reported in eleven of 98 patients with T-cell lymphoma and were associated with TET2 mutations (Couronne et al., 2012).

T-cell acute lymphoblastic leukemia (T-ALL)

Note

DNMT3A mutations were detected in 16 of 90 patients (17.8%) with T-ALL.

These alterations were associated with normal karyotype, lower hemoglobin levels and mutually exclusive in cases with CDKN2A/CDKN2B deletions. Further, these mutations had a strong association with shorter overall survival (Grossmann et al., 2013).

Lung cancer

Note

Deletion of Dnmt3a significantly promotes tumor growth and progression in lung cancer mouse model, suggesting that this gene may act like a tumor-suppressor gene and may be a crucial factor of lung cancer malignancy (Gao et al., 2011).

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