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Gene Section
Review

NNMT (nicotinamide N-methyltransferase)

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Identity

Other names: EC 2.1.1.1

HGNC (Hugo): NNMT

Location: 11q23.2

DNA/RNA

Description

The human NNMT gene is approximately 16,5 kb in length, consists of 3 exons and 2 introns, and is mapped to chromosome 11q23.1. The first intron is 1,240 bp in length, while the second is approximately 14 kb long. The sequence of the 5'-untranslated region (UTR) of the NNMT cDNA is present in exon 1, while the sequence of the cDNA 3'-UTR is present in exon 3 (Aksoy et al., 1995). The initiation of transcription for the human NNMT gene occurs at or near a nucleotide located -108 bp upstream from the translation initiation codon and approximately 30 nucleotides 3'-downstream from an atypical TATA box element (TCTAAA) (Aksoy et al., 1995). The 3'-UTR ends with a poly(A) tract, and the polyadenylation signal ATTAAA is located 19 nucleotides upstream from the poly(A) region (Aksoy et al., 1994).

A strong promoter is located within the initial 700 bp of 5'-flanking sequence of the human NNMT gene (Yan et al., 1999).

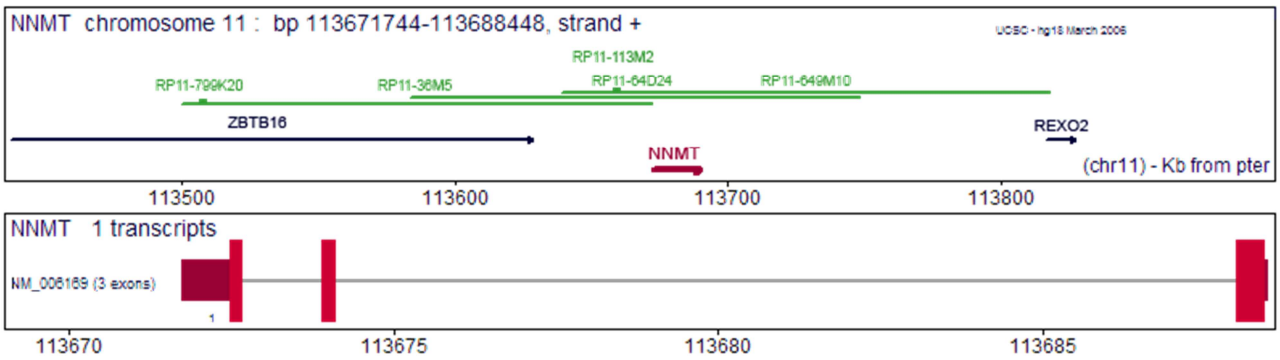
Transcription

Transcription of the human NNMT gene produces a full-length mRNA transcript of 1,579 bp.

It was recently shown that NNMT expression in some thyroid cancer cells may be regulated by hepatocyte nuclear factor beta (HNF-1beta).

HNF-1beta is able to function as a transcription activator of NNMT promoter, binding to specific sites in the basal promoter region (between nucleotides -148 and -162 relative to the translation initiation codon) (Xu et al., 2005).

In BHP 18-21 papillar thyroid cancer cells, the histone deacetylase inhibitor depsipeptide reduces NNMT mRNA level through down-regulation of transcription activator HNF-1beta (Xu et al., 2006).



Structure of human Nicotinamide N-methyltransferase (NNMT) gene and transcript. NNMT gene is encoded on 3 exons which span 16,704 bp at chromosome 11 (nucleotides 113,671,745-113,688,448). Exons are depicted as red boxes separated by intron sequences (solid lines). Brown boxes contain the untranslated sequences (5'-UTR and 3'-UTR).

Enhanced NNMT expression has been also correlated to activation of STAT3 in Hep-G2 liver cancer cells stimulated with IL-6 and in colorectal cancer tissues (Tomida et al., 2008).

Pseudogene

No pseudogene of NNMT was reported in human.

Protein

Note

The NNMT gene encodes a full-length monomeric protein of 264 amino acids with a predicted molecular weight of 29.6.

Description

Nicotinamide N-methyltransferase (NNMT, EC 2.1.1.1) is an S-adenosyl-L-methionine (Ado-Met) - dependent enzyme that catalyzes the methylation of nicotinamide and other pyridines to form pyridinium ions (Rini et al., 1990).

NNMT was first identified by cDNA cloning from the liver and the protein is predicted to be present in the cytosol (Aksoy et al., 1995).

A radiochemical microassay was developed by Rini et al. (1990) to study selected characteristics of NNMT activity in human liver preparations.

These studies suggested that human hepatic NNMT is a cytoplasmic enzyme with a pH optimum of approximately 7.4. Apparent K_m values for its two substrates, nicotinamide and S-adenosyl-L-methionine, are 347 and 1.76 µmol/l, respectively. The enzyme activity is inhibited by the reaction products, N^1-methylnicotinamide and S-adenosyl-L-homocysteine, while its activity is not affected by inhibitors of other methyltransferases. Basal enzyme activities, detected in human liver biopsy samples, show large individual variations with a bimodal frequency distribution.

Aksoy et al. (1994) set out to clone and express a cDNA for human liver NNMT to study molecular mechanisms involved in the regulation of individual differences of NNMT activity in humans. The cloning strategy involved purification of human liver NNMT, leading to partial amino acid sequence, followed by direct PCR-based cloning with the use of the rapid amplification of cDNA ends (RACE). The combined use of these techniques resulted in the isolation of a human liver NNMT cDNA that was 969 bp long, with a 792-bp open reading frame that encoded a 264-amino acid protein with a calculated molecular mass of 29,600 Daltons. Transient expression of the protein encoded by this cDNA demonstrated that it catalyzed the methylation of nicotinamide and had biochemical characteristics similar to, or identical with, those of human liver NNMT.

Recently, 2-DE experiments revealed that NNMT exists in multiple spots in gastric tissues and the presence of multiple NNMT spots is highly specific to cancer tissues of stomach. This suggests that NNMT could receive a post-translational modification in cancer-specific manner, but the mechanism by which NNMT is modified is still unknown (Lim et al., 2006).

Expression

NNMT is predominantly expressed in the liver, while a lower expression has been detected in the kidney, lung, skeletal muscle, placenta, heart, and brain. The N-methylation of nicotinamide is known to be altered in some diseases including Parkinson's disease (Green et al., 1991), hepatic cirrhosis (Cuomo et al., 1994), COPD (chronic obstructive pulmonary disease) (Debigarè et al., 2008), atherosclerosis (Mateuszuk et al., 2009), etc. The abnormal expression of NNMT has been identified in several kinds of tumors, such as glioblastoma (Markert et al., 2001), stomach adenocarcinoma (Jang et al., 2004; Lim et al., 2006), papillary thyroid cancers (Xu et al., 2003; Xu et al., 2005), renal carcinoma (Yao et al., 2005; Sartini et al., 2006), oral squamous carcinoma (Sartini et al., 2007), colorectal cancer (Roessler et al., 2005), hepatocellular carcinoma (Kim et al., 2009), bladder cancer (Wu et al., 2008), lung cancer (Tomida et al., 2009) and pancreatic cancer (Rogers et al., 2006).

Localisation

NNMT is a cytosolic enzyme.

Function

NNMT is an important cytosolic methyltransferase, belonging to Phase II Metabolizing Enzymes. The enzyme catalyzes the N-methylation of nicotinamide, pyridines and other structural analogs, playing a crucial role in the biotransformation and detoxification of many xenobiotic compounds. In fact, the metabolism of drugs, toxic chemicals, hormones, and micronutriens is an important topic in the fields of pharmacology and endocrinology, and it is often implicated in many diseases and pathophysiological processes, such as cancer and resistance to chemotherapy (Szakàcs et al., 2004). N-methylation is one method by which drugs and other xenobiotic compounds are metabolized by the liver and the enzyme NNMT is responsible for this activity which uses S-adenosyl-L-methionine as the methyl donor. The NNMT reaction yields two products: S-adenosyl-L-homocysteine and N^1-methylnicotinamide. S-adenosyl-L-homocysteine is converted into homocysteine by S-adenosyl-L-homocysteine hydrolase. N^1-methylnicotinamide is mostly excreted into urine and partly further converted via catalysis by aldehyde oxidase to N^1-methyl-2-pyridone-5-carboxiamide and N^1-methyl-4-pyridone-5-carboxiamide, which are also excreted into urine. N-methylation has been proposed as a metabolic pathway for nicotinamide excretion, and NNMT is the only enzyme known to utilize nicotinamide as methyl acceptor substrate. Therefore, NNMT could participate in the regulation of nicotinamide intracellular levels, modulating its excretion after N-methylation.

Nicotinamide, the amide of nicotinic acid, is the precursor of the coenzyme beta-nicotinamide adenine dinucleotide (NAD), an essential cofactor for several oxidoreductases, which participates in a wide range of biological processes, including energy supply, cellular resistance to stress or injury, and longevity (Williams et al., 2005). In addition, several enzymes, which use NAD as substrate can be inhibited by nicotinamide. Because of this type of product inhibition, the salvage and/or elimination of nicotinamide are crucial steps in NAD metabolism and the enzyme NNMT could be involved in controlling these cellular events. NNMT activity may also play a role in regulating biological processes related to N^1-methylnicotinamide. It has recently become apparent that it possesses anti-inflammatory (Bryniarski et al., 2008), anti-thrombotic (Chlopicki et al., 2007), vasoprotective (Bartus et al., 2008), and gastroprotective (Brzozowski et al., 2008) properties. NNMT was characterized by Cantoni in 1951 (Cantoni et al., 1951) and it is highly expressed in liver where its activity displays a 5-fold variation among individuals and has a bimodal frequency distribution. This observation raises the possibility that this enzyme activity may be regulated by a genetic polymorphysm. Such a polymorphism could have functional implications for individual differences in the metabolism and therapeutic effect of drugs (Aksoy et al., 1994) and in the formation of potentially toxic pyridine metabolites. Moreover, heightened NNMT activity was reported in many kinds of tumours. The up-regulation of this enzyme suggests a possible role of NNMT in cancer growth, migration, and metastasis (Sartini et al., 2007; Wu et al., 2008). However, the biological significance of alterations in NNMT activity in various pathological conditions remains largely unknown.

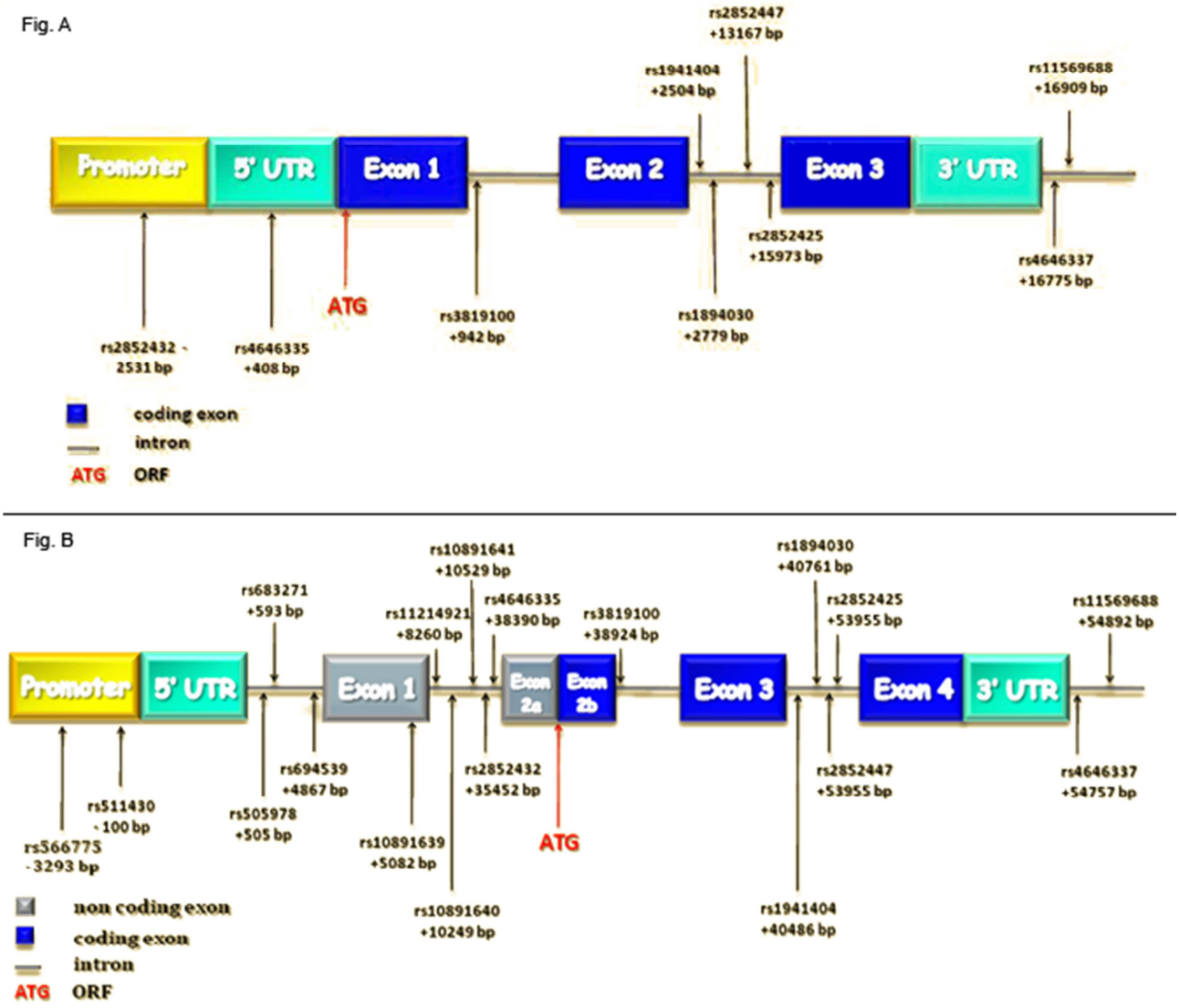
Homology

NNMT belongs to the NNMT/PNMT/TEMT family. The amino acid sequence of the protein encoded by human liver NNMT cDNA is 52% identical to that of mouse thioether S-methyltransferase (TEMT) and 37, 39, 38 and 39% identical to those of human, rat, mouse, and bovine phenylethanolamine N-methyltransferase (PNMT), respectively (Aksoy et al., 1994).
Human NNMT shows a very high level of identity to other non-human NNMTs: Sus scrofa (88%), Rattus norvegicus (87%) and Mus musculus (85%).

Mutations

In humans NNMT is highly polymorphic. About a hundred of polymorphisms, most of which are SNPs, have been identified. The figure A below shows the positions of investigated NNMT polymorphisms, taking as a reference the start site of transcription in 5'UTR region.
An alternative NNMT gene organization is available at UCSC web site. This sequence, depicted in the figure B below, displays another putative 5'UTR region located at 38,732 bp upstream of the open reading frame.
NNMT is one of at least 39 SAM-dependent methyltransferases and is involved in different metabolic pathways such as folate and homocysteine ones. Several independent studies have investigated some NNMT polymorphisms that could reflect differences in catalytic activity or in transcriptional efficiency of gene; however data available in literature are contrasting because some archived SNPs are very rare substitutions or limited to some ethnic group. Yan (Yan et al., 1999) and Smith (Smith et al., 1998) detected no association between SNPs (either insertion/deletion events within exons or into 5' flanking region) and NNMT activity variation in healthy population. Saito (Saito et al., 2001) suggested that some SNPs in the NNMT 5' flanking region may influence its transcriptional efficiency. Several studies about association between NNMT genetic variations and alteration of cellular pathways are present in literature.

Homocysteine (Hcy) pathway. In humans, the only source of Hcy is the demethylation of methionine, through several methyl transferase activities, such as NNMT. Hyperhomocysteinemia is a condition characterized by high plasma level of Hcy and it is implicated in several diseases, as Alzheimer and other clinical status such as atherosclerosis, ischemic strokes (Furie et al., 2006) and osteoporosis. The causes of hyperhomocysteinemia are both genetic and environmental (e.g.: life-style, sex, age), but genetic basis are still poorly understood. Different studies have investigated an association of NNMT polymorphisms with hyperhomocysteinemia. Souto (Souto et al., 2005) carried out the GAIT (Genetic Analysis of Idiopathic Thrombophilia) Project in a Spanish population, where 10 SNPs of NNMT gene were investigated. The results of this study suggested a strong correlation between plasma Hcy level and a specific haplotype. Because these genetic variants are in non-coding regions, they could influence the regulation of transcription but evidence on the functionality of the NNMT polymorphisms is still conflicting.
A consistent study was carried out by Ling Zhang (Zhang et al., 2007) in about three hundred healthy japanese workers. Authors focused on a specific NNMT polymorphism (rs694539) localized in the first intron. The results confirmed that SNPs in non-coding regions affected the regulation of transcription, but they weren't the main determinant



of the plasma Hcy levels, because other factors were involved: age, sex, plasma folate levels and the associations with MTHFR polymorphisms.
The association between NNMT polymorphisms and hyperhomocysteinemia has been investigated by Bathum (Bathum et al., 2007). Six hundred and three danish adult twin pairs were included in the study. Experimental results suggested that MTHFR C677T is the only SNP responsible for the disease progression, leaving only minor influence to other genetic variations.

Implicated in

Thyroid cancer

Note

Gene expression profiles obtained by DNA microarray showed NNMT overexpression in papillary thyroid carcinoma cells, but not in primary goiter cell O4 and in other cancer cell lines (follicular, medullary, and anaplastic). The results were validated using RT-PCR and Northern Blot analysis. High levels of NNMT enzyme activity were detected in eight of ten papillary lines, and in three of six of the follicular cell lines tested, while in the anaplastic and medullary cancer cell lines, as well as in primary thyroid cultures, and normal thyroid tissue enzyme activity was low or undetectable. Immunohistochemical staining of human papillary carcinoma specimens for NNMT showed positive and strong staining in 94% of the specimens, but not in the normal follicular cells (Xu et al., 2003). Even though the molecular mechanism leading to NNMT over-expression is at present unknown, the hepatocyte nuclear factor-1beta (HNF-1beta), expressed in many papillary cancer cell lines, seems to be involved in the activation of NNMT transcription (Xu et al., 2005). Moreover, the repression of NNMT observed in BHP 18-21 papillar thyroid cancer cells treated with depsipeptide, a histone deacetylase inhibitor, is at the transcription level through downregulation of transcription activator HNF-1beta (Xu et al., 2005).

Gastric cancer

Note

The differential proteome profile of gastric cancer obtained through a series of 2-DE experiments combined with peptide mass finger printing analysis by MALDI-TOF mass spectrometry showed overexpression of NNMT in tumour tissues compared to the adjacent normal mucosa. Moreover, Western Blot revealed that NNMT exists as a single spot in gastric tissue, while four to five spots (with different pI values and similar MW) were detected in most gastric tumour tissues. The pattern of multiple NNMT spots is highly specific to tumour tissue and might lead to hypothesize that NNMT in gastric cancer carries a post-translational modification, possibly phosporylation (Jang et al., 2005; Lim et al., 2006).

Colorectal cancer

Note

Roessler et al. (2005) found that NNMT is upregulated in malignant tissues compared with normal colonic epithelium and they suggested that NNMT serum levels could be useful as a biomarker in the early detection of patients with colorectal cancer. In addition, immunostaining of NNMT and phospho-Stat3 in colon cancer tissues showed that enhanced expression of NNMT is correlated with activation of Stat3 (Tomida et al., 2008).

Renal cell carcinoma

Note

Elevated levels of NNMT mRNA were first detected in clear cell renal cell carcinoma (RCC) by Yao et al. (2005), who examined the gene expression profiles of several normal kidneys and several cancerous specimens, although adjacent normal tissue was not available. NNMT expression was further investigated in paired tissue samples from cancerous and non-cancerous parts of the kidneys of patients with clear cell /chromophobe renal cell carcinoma and with oncocytoma. The authors observed significant NNMT overexpression in 100% of ccRCCs tested, with 41-fold higher mean expression in cancerous tissue than in adjacent non-cancerous tissue. In keeping with NNMT mRNA level results, in ccRCC NNMT protein was found upregulated, and a marked increase in its enzymatic activity was detected (Sartini et al., 2006). The increase in the level of NNMT correlated inversely with tumour size, thus suggesting that NNMT activity may be significant in an early stage of malignant transformation.

Prognosis

NNMT mRNA levels did not correlate with survival (Yao et al., 2005).

Oral cancer

Note

Compared with normal mucosa, favorable oral squamous cell carcinomas (OSCCs) (N0) exhibited significantly increased expression of NNMT, while no marked enzyme expression alterations between tumour and adjacent normal mucosa were detected in most of the unfavorable OSCCs (N+). The low NNMT expression detected in subjects with metastasis supports the hypothesis that NNMT plays a role in tumour expansion, and tumours which downregulate this enzyme may be able to evade immunosurveillance and grow.

Prognosis

NNMT mRNA levels appear to be inversely related to pT and pathological staging, suggesting the possibility of this enzyme as a prognostic factor (Sartini et al., 2007). Kaplan-Meier analysis shows an improved overall survival rate for patients bearing tumours with higher NNMT expression levels than patients with tumours with lower NNMT expression, although without reaching statistical significance (Emanuelli et al., 2009, in press).

Insulinoma and pancreatic cancer

Note

NNMT was found to be downregulated in human insulinoma, when compared with normal islets preparations. Its underexpression was associated with reduced TGFbeta1 mRNA levels, being NNMT a target gene of this cytokine, which acts via the activation of Smad proteins (Nabokikh et al., 2007). Conversely, NNMT seems to be overexpressed in the malignant pancreatic ductal carcinoma. Gene expression alterations were explored by profiling the RNA isolated from pancreatic juice of patients with pancreatic cancer and patients with non-neoplastic disease (Rogers et al., 2006).

Lung cancer

Note

Patients with non-small cell lung cancer (NSCLC) exhibit increased NNMT serum levels compared to patients with chronic obstructive pulmonary disease (COPD) and healthy donors (Tomida et al., 2009). ROC curves were employed to evaluate the sensitivity and specificity of NNMT serum levels measurement for the detection of lung cancer. The results obtained seem to indicate that NNMT is slightly better than the currently available lung cancer biomarker CEA, although both the sensitivity and specificity displayed appear relatively low. No significant correlation between NNMT and CEA serum levels were found. Therefore, the measurement of serum levels of both markers could contribute to improve sensitivity for detection of NSCLC.

Liver cancer

Note

A large number of Hepatocellular carcinoma (HCC) specimens were analyzed by real-time reverse

transcription PCR. NNMT mRNA level appeared markedly reduced in tumour samples compared to the surrounding healthy tissue. Moreover, NNMT expression was significantly associated with tumour stage.

Prognosis

NNMT mRNA levels appear to be inversely related to overall survival time as well as to disease-free survival time, suggesting the posssibility of this enzyme as a prognostic factor (Kim et al., 2009). It has been found that nuclear factor-interleukin 6 and STAT3 induce NNMT promoter activity in the transformed Hep-G2 cells (Tomida et al., 2008). Therefore, the prognostic power of NNMT mRNA level determination could be improved by the simultaneous measurement of related regulatory molecules (Kim et al., 2009).

Bladder cancer

Note

NNMT expression in the radioresistant bladder carcinoma cell line MGH-UI has been reported to be higher than that observed in its radiosensitive subclone S40b (Kassem et al., 2002). The NNMT possible involvement in determining radioresistance might be related to its catalytic activity, which could lead to a decrease of intracellular levels of nicotinamide, compound known as a radiosensitizer able to enhance the damage produced by radiation treatments.

Prognosis

Recently, transcriptional profiling of several bladder cancer cell lines and human bladder cancers identifies NNMT as gene involved in cancer migration, while being associated with tumour stage in patients. Moreover, NNMT silencing appears to decrease cell proliferation, making the enzyme a promising target for chemotherapy (Wu et al., 2009).

Acute lymphoblastic leukemia (ALL)

Note

Folate pathway. Folate metabolism is essential for cellular functioning because it provides methyl donors for some important biochemical reactions such as methylation of homocysteine. Genetic variations of some folate related genes have been associated with low folate levels, influencing the risk of cancer.

de Jonge (de Jonge et al., 2009) investigated the association between folate pathway polymorphisms and susceptibility to lymphoid leukemia in 245 pediatric ALL patients. Authors demonstrated that specific polymorphisms of MTHFR (C677T), RFC1 (G80A) and NNMT (IVS C-151T) and their association are related to ALL risk. Specifically, NNMT IVS -151TT and NNMT IVS -151 CT+TT/ RFC1 80AA subjects showed a 2,2 and 4,2-fold increased ALL risk, respectively, while NNMT IVS -151CC/ MTHFR 677CT+TT patients exhibited a 2-fold reduction in ALL risk. Authors suggested that the mechanism of this increased risk is related to a reduction of cellular folate uptake and change in methylation status.

Chronic obstructive pulmonary disease (COPD)

Note

Chronic obstructive pulmonary disease (COPD) is an inflammatory disorder characterized by progressive bronchial obstruction and often associated with peripheral muscle wasting. Microarray analysis performed on vastus lateralis muscle tissue revealed that NNMT was up-regulated (5.8-fold than normal subjects) in patients with COPD and muscle atrophy. Real-Time PCR analysis confirmed an higher expression of NNMT in patients with COPD. Statistical analysis revealed a positive correlation between NNMT deltaC_t and FEV_1 (forced expiratory volume in 1 s). This correlation suggests that the airway obstruction, through NNMT up-regulation, could lead to an alteration of energy metabolism in these patients (Debigarè et al., 2008).

Parkinson's disease

Note

NNMT has been recently demonstrated to be present in the brain with a regional distribution, being in relatively high concentration in spinal cord and cortex and present in lower concentration in substantia nigra. In Parkinson's Disease (PD) brain, NNMT is present in increased concentrations. This enhanced NNMT activity seems to be responsible for the production of toxic N-methylpiridinium compounds that have been advanced as possible neurotoxins underlying nigrostriatal degeneration. In fact the enzyme displays a wide substrate specificity that enables it to convert a large range of substrates to their corresponding pyridinium ions, involved in Complex I poisoning, which leads to diminished ATP production. This reduced ATP synthesis may be also related to NNMT upregulation, in that high enzyme levels lower the amount of nicotinamide available for NADH synthesis (Williams and Ramsden, 2005; Williams et al., 2005).

Abdominal aortic aneurysm (AAA)

Note

NNMT and its genetic variants are candidate risk factors for AAA.

Giusti and co-workers, using a multiplex PCR oligonucleotide extension approach (Giusti et al., 2008b), investigated the correlation between some genetic variants of fifteen genes involved in the methionine metabolism (including NNMT) and AAA (Giusti et al., 2008a) in 423 subjects affected from AAA. They demonstrated that only seven genes, including NNMT, have at least one specific haplotype that represents a probable risk factor for AAA. They found also that the influence of the single gene in this pathology is independent from the role in homocysteine metabolism.

Spina bifida

Note

Moderate hyperhomocysteinemia is a risk factor for Neural Tube Defects (NTDs).

Several SNPs of NNMT gene have been analysed in 252 cases (infants with spina bifida) and 335 controls (non malformed infants) by Lu (Lu et al., 2008). Findings showed no association between any single genetic variation and NTDs. Only a specific haplotype was significantly associated with decreased risk for spina bifida in non Hispanic Whites.

Congenital heart defects (CHDs)

Note

CHDs seem to be multifactorial phenomenon due to polymorphisms of NNMT gene, maternal nutrition and medicine use in the peri-conception period.

van Driel (van Driel et al., 2008) investigated the SNP rs694539, probably involved in the regulation of NNMT transcription (Souto et al., 2005). In the analyses, he included two hundred and ninety-two cases and three hundred and sixteen control families. No association between NNMT polymorphism and risk of CHDs was detected. On the other hand, children with the combination of heterozygous or mutant genotype for rs694539, peri-conception medicine use and low dietary nicotinamide intake showed eight-fold increased risk for CHDs.

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