Gene Section
Review

DDC (dopa decarboxylase (aromatic L-amino acid decarboxylase))

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Identity

Other names: AADC

HGNC (Hugo): DDC

Location: 7p12.1

Local order: Centromere to telomere.

DNA/RNA

Note

The complete nucleotide structure of the human DDC gene has been determined from tissues of neural and non-neural origin (Sumi-Ichinose et al., 1992; Ichinose et al., 1992). The full DDC cDNA sequence has been cloned from human cells, such as pheochromocytoma (Ichinose et al., 1989), liver (Ichinose et al., 1992), hepatoma cells (Scherer et al., 1992), placenta (Siaterli et al., 2003), peripheral leukocytes (Kokkinou et al., 2009b), as well as from several human cell lines, such as, U937 macrophage cells (Kokkinou et al., 2009a), SH-SY5Y, HTB-14 and HeLa cells (Chalatsa et al., 2011).

Description

The human DDC gene exists as a single-copy in the haploid genome. It is composed of 15 exons and 14 introns, spanning for more than 85 kbs (Sumi-Ichinose et al., 1992). The size of the exons was found to range from 20 to 406 bps (Sumi-Ichinose et al., 1992), whereas the size of the introns ranged from 927 to 24077 bps (Sumi-Ichinose et al., 1992; Yu et al., 2006). The DDC gene is located in close proximity to the epidermal growth factor (EGF) gene (Craig et al., 1992).

Transcription

Alternative splicing events are responsible for the production of two distinct DDC mRNAs, termed neural and non-neural, which differ in their 5' untranslated region (UTR). The neural-type transcript includes exon N_1 (83 bps) that is located 17.8 kbs upstream of exon two. The non-neural type DDC mRNA bears exon L_1 (200 bps), which is located 4.2 kbs upstream to the location of exon N_1. The second exon contains the translation start site and is located 22 kbs downstream from the non-neural (L_1) exon (Ichinose et al., 1992). The transcription of the gene starts at position -111 (Sumi-Ichinose et al., 1992).

It has been reported that the two alternative DDC transcripts share identical coding regions and that their production is a result of alternative splicing and alternative promoter usage (Ichinose et al., 1992; Sumi-Ichinose et al., 1995). Neural and non-neural promoters have been identified 5' to the flanking region of the respective exon 1 (Le Van Thai et al., 1993; Sumi-Ichinose et al., 1995; Chatelin et al., 2001; Dugast-Darzacq et al., 2004). The generation of the two alternative DDC mRNAs is not a mutually exclusive and tissue-specific event as previously thought (Siaterli et al., 2003; Vassilacopoulou et al., 2004; Kokkinou et al., 2009a; Kokkinou et al., 2009b; Chalatsa et al., 2011).An alternative splicing event has been described within the coding region of DDC mRNA, leading to the formation of a shorter transcript lacking exon 3 (O'Malley et al., 1995; Chang et al., 1996).

DDC mRNA transcripts	Expressed in human tissues, cells and cancer cell lines
Neural and non-neural full-length *DDC* mRNAs	kidney (Siaterli *et al.*, 2003)
	placenta (Siaterli *et al.*, 2003)
	peripheral leukocytes (Kokkinou *et al.*, 2009a)
Neural-type *DDC* mRNA, lacking exon 3	peripheral leukocytes (Kokkinou *et al.*, 2009a)
	T-lymphocytes (Kokkinou *et al.*, 2009a)
	U937 histiocytic lymphoma cell line (Kokkinou *et al.*, 2009b)
Neural full-length and neural lacking exon 3 *DDC* mRNAs	SH-SY5Y (neuroblastoma, of neural origin) (Chalatsa *et al.*, 2010)
Non-neural full-length and neural lacking exon 3 *DDC* mRNAs	HeLa (Cervical adenocarcinoma) (Chalatsa *et al.*, 2010)
	HTB-14 (Glioblastoma, Astrocytoma) (Chalatsa *et al.*, 2010)
Neural Alt-*DDC* mRNA	placenta (non-neural tissue) (Vassilacopoulou *et al.*, 2004)
	kidney (non-neural tissue) (Vassilacopoulou *et al.*, 2004)

Table 1. Expression of DDC mRNA transcripts in human tissues, cells and cancer cell lines.

It must be noted that the above authors did not specify the nature, neural or non-neural, of this shorter transcript. Recent evidence have revealed the neural nature of this alternative transcript in humans (Kokkinou et al., 2009a; Kokkinou et al., 2009b; Chalatsa et al., 2011).

A novel DDC mRNA coding region splice-variant, resulting in the formation of a truncated DDC mRNA has been also identified. This human DDC mRNA (1.8 kbs), termed as Alt-DDC, lacks exons 10-15 of the full-length transcript, but includes an alternative exon 10 (Vassilacopoulou et al., 2004). The Alt-DDC exon 10 (358 bps) was found within intron 9 of the DDC gene. Although Alt-DDC mRNA was detected in human placenta, high expression levels of this alternative transcript were found in human kidney (Vassilacopoulou et al., 2004).

The notion that transcription of the human DDC gene leads to the production of multiple mRNA isoforms, which are expressed in a non-mutually exclusive and tissue-specific manner, underlines the complexity of the expression patterns of this gene (table 1).

Pseudogene

None has been identified yet.

Protein

Note

Although, it was initially suggested that the DDC gene encoded for a single protein product (Sumi-Ichinose et al., 1992), evidence that demonstrated the expression of additional DDC protein isoforms in humans, argue against it (O'Malley et al., 1995; Chang et al., 1996; Vassilacopoulou et al., 2004).

Description

The DDC enzyme (EC 4.1.1.28) was initially purified and characterized from pig kidney (Christenson et al., 1970) as well as from the insects Calliphora vicina (Fragoulis and Sekeris, 1975) and Ceratitis capitata (Mappouras and Fragoulis, 1988; Bossinakou and Fragoulis, 1996). DDC is a homodimer of 100-110 kDa, with a subunit molecular mass of 50-55 kDa (Voltattorni et al., 1979; Mappouras et al., 1990; Bossinakou and Fragoulis, 1996). The full-length protein molecule consists of 480 amino acids (Ichinose et al., 1989). DDC is a pyridoxal-5-phosphate (PLP)-dependent enzyme possessing a single binding-site for PLP per subunit (Voltattorni et al., 1982; Ichinose et al., 1989; Burkhard et al., 2001).

Expression of the DDC gene, in humans, results in the production of additional protein isoforms (O'Malley et al., 1995; Chang et al., 1996; Vassilacopoulou et al., 2004). O'Malley et al. (1995) identified of a new DDC protein isoform (O'Malley et al., 1995). The truncated DDC protein isoform (Mr; 50 kDa) consists of 442 amino acid residues (DDC$_{442}$). This isoform was found to be inactive towards the decarboxylation of both L-Dopa to Dopamine and 5-Hydroxytryptophan (5-HTP) to serotonin (O'Malley et al., 1995). As mentioned above, the translation of Alt-DDC mRNA resulted in the synthesis of a truncated 338 amino acid long polypeptide, termed as Alt-DDC (Mr; 37 kDa). This isoform was identical to the full-length DDC protein up to amino acid residue 315. The remaining 23 amino acids of the C-terminal sequence are encoded by the alternative DDC exon 10 and are not incorporated in

Source of DDC	Identity:					
	Bovine	Porcine	Rat	Guinea-pig	*Drosophila*	*C.Capitata*
Human	88.5%	88.7%	88.5%	86.8%	58.9%	45%

Table 2. Human DDC identity.

the full-length DDC protein sequence (Vassilacopoulou et al., 2004).

Although previous data had suggested that DDC was a rather unregulated molecule, several findings have indicated that DDC activity can be modulated by many factors, such as D1, DA receptor antagonists (Rossetti et al., 1990), a_2-adrenergic receptor antagonists (Rossetti et al., 1989), D1, D2 receptor antagonists (Zhu et al., 1992; Hadjiconstantinou et al., 1993), DA receptor agonists (Zhu et al., 1993), PK-A and PK-C mediated pathways (Young et al., 1993; Young et al., 1994) and by endogenous inhibitors isolated from human serum (Vassiliou et al., 2005) and placenta (Vassiliou et al., 2009).

Expression

DDC has been detected throughout the length of the gastrointestinal tract (Eisenhofer et al., 1997) and in blood plasma (Boomsma et al., 1986). DDC is expressed in normal human kidney and placenta (Mappouras et al., 1990; Siaterli et al., 2003). DDC expression was observed in normal peripheral leukocytes and T-lymphocytes (Kokkinou et al., 2009b). Furthermore, DDC is expressed in the human cancer cell lines U937 (Kokkinou et al., 2009a), SH-SY5Y, HeLa and HTB-14 (Chalatsa et al., 2011). Interestingly, the expression of the alternative DDC isoform (Alt-DDC) was also demonstrated in peripheral leukocytes (Kokkinou et al., 2009b), U937 (Kokkinou et al., 2009a), SH-SY5Y and HeLa cell lines (Chalatsa et al., 2011).

In the central nervous system, increased DDC enzymatic activity is detected in the hypothalamus, epiphysis, striatum, locus ceruleus, olfactory bulb and retina (Park et al., 1986). Elevated enzymatic DDC activity is also detected in peripheral organs such as liver, pancreas, kidney, lungs, spleen, stomach, salivary glands, as well as in the endothelial cells of blood vessels (Lovenberg et al., 1962; Rahman et al., 1981; Lindström and Sehlin, 1983).

Localisation

DDC was considered to be a cytosolic molecule (Lovenberg et al., 1962; Sims et al., 1973).

Nevertheless, additional experimental findings have demonstrated that a population of enzymatically active DDC molecules is associated with the cellular membrane fraction in the mammalian CNS (Poulikakos et al., 2001). Membrane-associated, enzymatically active DDC subpopulations were detected in the highly hydrophobic fractions of normal human leukocytes and U937 cancer cells (Kokkinou et al., 2009a; Kokkinou et al., 2009b).

Function

In terms of substrate specificity, the DDC molecule purified from insects demonstrated a remarkably high affinity towards the decarboxylation of L-Dopa to dopamine (Fragoulis and Sekeris, 1975; Mappouras and Fragoulis, 1988; Bossinakou and Fragoulis, 1996). However, work by Mappouras et al. (1990) in the normal human kidney has suggested that the enzyme is capable of also decarboxylating L-5-Hydroxytryptophan to serotonin, although the decarboxylation activity towards L-5-Hydroxytryptophan was found to be considerably lower than the one observed for L-Dopa (Mappouras et al., 1990). Since DDC expression results in the production of multiple protein isoforms, it is conceivable that these different protein molecules could be responsible for the decarboxylation of other aromatic L-amino acids.

Homology

Comparison of the amino acid sequence of DDC from different species, suggested that the enzyme is an evolutionarily conserved molecule. The amino acid sequence around the coenzyme binding lysine is also evolutionarily conserved (Bossa et al., 1977; Ichinose et al., 1989). The conserved amino acids are residues 267-317, which surround the PLP-binding site (Ichinose et al., 1989), as well as, the extended regions of amino acids 64-155 and 182-204, which according to Maras et al. (1991) are important for the enzyme's catalytic function (Maras et al., 1991). Table 2 shows the percentage of human DDC amino acid identity to other species (Maras et al., 1991; Mantzouridis et al., 1997).

Mutations

Mutations	Amino acid change	Exon number
1222C>A	L408I	13
19C>T	R7X	2
140C>A	P47H	2
1040G>A	R347Q	11
749C>T	S250F	7
304G>A	G102S	3
925T>C	F309L	9
439A>C	S147R	5
272C>T	A91V	3
823G>A	A275T	8
853C>T	R285W	8
1303C>T	R412W	13
c.387 G->A	G102S	3
1367insA	I433fsX492	14
127delC	P43fsX20	2
IVS6+4A>T	M239fsX250	6 and 7

Table 3. The mutations of the DDC gene in the AADC disorder.

Germinal

Such mutations have not been identified so far.

Somatic

Aromatic L-amino acid decarboxylase (AADC) deficiency, a rare autosomaly-recessive inherited defect, is associated with mutations of the DDC gene. This disorder leads to profound modifications in the homeostasis of central and peripheral nervous system (Hyland et al., 1992). In their majority, such mutations are missense and are listed above (table 3). Other mutations of the human DDC gene that are related to AADC-deficiency are also included (Fiumara et al., 2002; Chang et al., 2004; Pons et al., 2004; Tay et al., 2007; Lee et al., 2009).

Implicated in

Prostate cancer

Note

Neuroendocrine differentiation features have been identified in prostatic adenocarcinoma. Aggressiveness of the disease is increased as the cells reach the androgen-independent phase (Speights et al., 1997; Nelson et al., 2002). L-Dopa decarboxylase has been identified as a novel androgen receptor (AR) coactivator protein (Wafa et al., 2003). Recent evidence have shown that the expression of DDC mRNA could serve as a potential novel biomarker in prostate cancer (Avgeris et al., 2008). Wafa et al. (2007) have indicated by immunohistochemistry that DDC was found to be a putative neuroendocrine marker for prostate cancer. In certain NE tumor cells of the prostate gland, DDC was found to be co-expressed with AR. DDC expression was increased after hormone-ablation therapy, as well as, in metastatic tumors that have progressed to the androgen-independent phenotypes (Wafa et al., 2007).

Disease

Increased DDC mRNA and/or elevated protein expression levels were detected in the LnCaP cell line following synthetic androgen treatment. DDC protein was found to be enzymatically active in the androgen-treated LnCaP cells as compared to the untreated controls. In treated LnCaP cells, DDC was up-regulated during AR-activation, while DDC expression was down-regulated following AR-inhibition. These findings support a coactivator role for DDC in AR activation (Shao et al., 2007). DDC over-expression affects the gene expression profile of the androgen-dependent prostate cancer cell line, LnCaP, as revealed by microarray analysis (Margiotti et al., 2007).

Prognosis

Statistically significant elevated DDC mRNA levels were observed in prostate cancer tissue specimens when compared to benign hyperplasia human samples. Multivariate survival analysis indicated that the expression of the DDC gene could be used as an independent marker for the differential diagnosis between prostate cancer and benign hyperplasia patients, using tissue biopsies. DDC mRNA expression was also shown to be associated with advanced tumor stage and higher Gleason score. This finding suggested an unfavorable prognostic value for DDC expression in patients with tumors in their prostate glands (Avgeris et al., 2008).

Colorectal carcinoma

Note

High L-Dopa decarboxylase activity has been detected in almost half of the original colorectal carcinomas examined, as well as, in the majority of cultured cell lines, established from human primary and metastatic tumors (Park et al., 1987). Other data have shown that most solid colorectal tumors exhibited DDC activity at lower levels when compared to the enzymatic DDC activity displayed by the NE tumors (Gazdar et al., 1988). DDC mRNA expression was found to be elevated in well-differentiated (grade I) intestinal adenocarcinomas as compared to more aggressive tumors (Kontos et al., 2010).

Prognosis

Increased DDC mRNA levels were observed in grade I colorectal adenocarcinomas. Survival analysis revealed a significantly lower risk of disease recurrence and longer overall survival for patients with DDC-positive

colorectal neoplasms. These results indicate that DDC mRNA expression might represent a possible future biomarker for the prognosis of colorectal cancer patients (Kontos et al., 2010).

Gastric cancer

Note

Advanced gastric cancer is characterized by peritoneal dissemination, the most common disease relapse, which is caused by the dispersal of free gastric cancer cells into the peritoneal cavity (Baba et al., 1989; Abe et al., 1995).

Disease

It has been proposed that increased DDC mRNA expression could be an accurate tool for the detection of gastric cancer micrometastases in the peritoneal cavity. According to Sakakura et al. (2004), DDC expression levels were equivalent to the degree of dissemination potential of gastric cancer cells.

Pheochromocytomas

Note

Pheochromocytomas are characterized by over-production of catecholamines (Eisenhofer et al., 2001).

Disease

These non-innervated tumors originate, in most cases, from adrenal medullary cells which are capable for catecholamine biosynthesis (Yanase et al., 1986). Catecholamine release by these cells is not initiated by nerve impulses. Elevated DDC mRNA levels have been detected in pheochromocytoma tissues as compared to normal adrenal medullary cells. Isobe et al. (1998) suggested that high DDC expression could lead to the development or growth of pheochromocytomas (Isobe et al., 1998).

Neuroblastomas

Note

In the neuroblastoma cell line, the SH-SY5Y cells, both neural full-length DDC mRNA and the neural mRNA isoform lacking exon 3, were detected (Chalatsa et al., 2011).

Disease

Neuroblastomas, the most common extracranial solid neoplasms in children, originate from sympathetic neural crest cells and their characteristic is the production of catecholamines and their metabolites (Boomsma et al., 1989). Neuroblastomas are categorized as small round-cell tumors of the childhood (Gilbert et al., 1999). In the active untreated state, plasma L-Dopa values and/or DDC enzymatic activity levels have been found to be elevated. Interestingly, following chemotherapy treatment, DDC enzymatic activity levels fall within the physiological range. Elevated levels of plasma L-Dopa and especially DDC enzyme activity are observed during disease relapse (Boomsma et al., 1989).

It is noted that conventional light microscopy cannot clearly differentiate between neuroblastoma and other small round-cell tumors of the childhood. Co-expression of DDC and Tyrosine Hydroxylase (TH) has been used for the differential diagnosis of these types of tumors (Gilbert et al., 1999).

Prognosis

Elevated levels of plasma L-Dopa, in neuroblastoma patients, could provide an indication for residual tumor. These findings could be associated with dismal prognosis for neuroblastoma patients. Furthermore, a sharp increase in plasma DDC enzymatic activity could be related to disease reccurence (Boomsma et al., 1989). DDC mRNA was detected in all bone marrow and peripheral blood samples obtained from neuroblastoma patients at relapse. Given these results, Bozzi et al. (2004) have suggested that DDC mRNA expression could represent a specific molecular marker for monitoring bone marrow and peripheral blood neuroblastoma metastases (Bozzi et al., 2004). Furthermore, DDC mRNA levels could be used as a sensitive indicator to predict minimal residual disease as well as the outcome for patients (Träger et al., 2008).

Lung carcinomas

Note

Elevated DDC enzymatic activity was observed in small-cell lung carcinoma (SCLC) as compared to normal lung epithelia (Nagatsu et al., 1985). The majority of non-SCLC (NSCLC) exhibited low levels or no DDC enzyme activity (Gazdar et al., 1981; Bepler et al., 1988). It is noted that in some NSCLC cases, high DDC activity values have been reported (Baylin et al., 1980), although in these lung lesions the detection of DDC activity was restricted to large-cell carcinomas and adenocarcinomas, while squamous cell carcinomas did not exhibit any enzymatic activity (Gazdar et al., 1988).

Disease

DDC activity appears to be a valuable neuroendocrine marker for identifying SCLC tumor cells in culture (Baylin et al., 1980). DDC enzymatic activity is highest during the exponential cellular growth phase and/or when the cells are during the transition from G_2 to the M phase of the cell cycle (Francis et al., 1983). DDC activity has been also used as a useful biomarker for the distinction of SCLC from NSCLC. Furthermore, DDC activity has been used for the differentiation between the classical SCLC cell lines (SCLC-C), which express high DDC activity levels, from the variant subtype of the SCLC (SCLC-V), which does not express the enzyme (Carney et al., 1985; Gazdar et al., 1985).

Prognosis

The elevated DDC enzymatic activity, which is observed in patients harboring SCLC tumors, seems to be associated with disease differentiation grade. High DDC activity has been associated with better prognosis and patient's outcome (Bepler et al., 1987).

Medullary thyroid carcinoma

Note

The expression of L-Dopa decarboxylase has been detected in medullary carcinoma of the thyroid gland (Pearse, 1969; Atkins et al., 1973).

Disease

Medullary thyroid carcinoma (MTC) originates from the calcitonin (CT)-secreting thyroid C cells and is a unique malignancy of endocrine origin (Tashjian and Melvin, 1968). Malignancy progression could be monitored, in patients with the virulent phenotype of the disease, using the simultaneous increased levels of DDC and histaminase (Trump et al., 1979; Lippman et al., 1982). It has been proposed that increased DDC enzymatic activity might represent an early differentiation marker in the virulent form of this neoplasm (Berger et al., 1984).

Neuroendocrine tumors (NETs): bronchial, liver and ileal carcinoids, gastric / pancreatic / pulmonary tumors

Note

DDC enzymatic activity constitutes an excellent cellular marker for identifying tumors of the neuroendocrine (NE) origin. The majority of NE tumors tested were found to express relatively high DDC enzymatic activity (Gazdar et al., 1988). DDC expression and/or activity have been reported in NETs, particularly in SCLC. For these reasons, DDC has been considered as a general endocrine marker (Gazdar et al., 1988; Jensen et al., 1990).

Disease

Strikingly higher DDC mRNA expression levels were revealed in all bronchial carcinoids and pulmonary NETs when compared to their normal corresponding types of tissues. Immunohistochemical data have confirmed DDC protein expression in all of these tumors. In the gastroenteropancreatic NETs examined, the detected DDC mRNA levels were comparable to those of normal gastric, ileal and pancreatic tissues. Almost half of the pancreatic and stomach NETs and all ileal carcinoids were found to be DDC immunoreactive (Uccella et al., 2006). Interestingly, hepatic carcinoid tumors demonstrated a 20-fold increase in DDC activity as compared with normal surrounding liver tissues (Gilbert et al., 1995).

Hybrid/Mutated gene

Not yet discovered.

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