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Gene Section
Review

DYRK1A (dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A)

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Identity

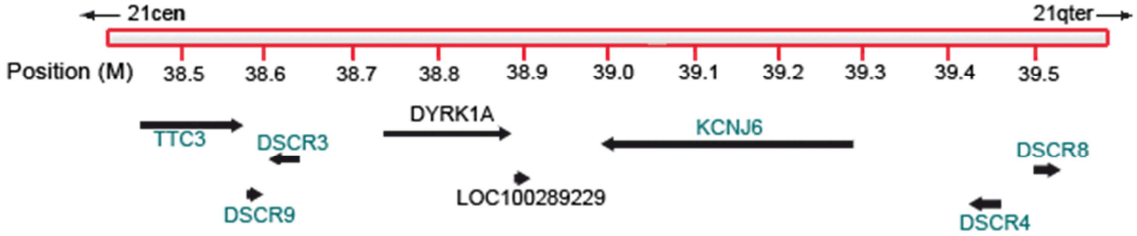
Other names: DYRK, DYRK1, HP86, MNB, MNBH

HGNC (Hugo): DYRK1A

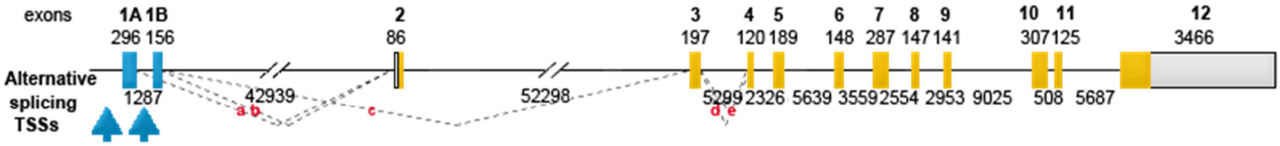
Location: 21q22.13

Local order:
Genes surrounding DYRK1A and their chromosome locations ordered from centromere to telomere (according to NCBI Map Viewer):
- TTC3 (tetratricopeptide repeat domain 3). Location 21q22.13.
- DSCR9 (Down syndrome critical region gene 9; miscRNA, non-protein coding). Location 21q22.13.
- DSCR3 (Down syndrome critical region gene 3). Location 21q22.13.
- **DYRK1A**. Location 21q22.13.
- LOC100289229 (hypothetical gene). Location 21q22.13.
- KCNJ6 (potassium inwardly-rectifying channel, subfamily J, member 6). Location: 21q22.1; 21q22.1.
- DSCR4 (Down syndrome critical region gene 4). Location 21q22.2.
- DSCR8 (Down syndrome critical region gene 8; miscRNA). Location 21q22.2.

Note
The chromosomal region depicted in the above figure is part of the "critical region" for Down syndrome, commonly named Down syndrome critical region (DSCR). This region, which encompasses 5.4 Mb of chromosome 21 and contains around 30 genes, has been defined in phenotype-genotype correlation studies of individuals with partial trisomy 21 (Delabar et al., 1993). Similar correlation studies of patients with partial monosomy 21 have defined a common region within DSCR that when deleted causes microcephaly and developmental delay. This region expands 1.2 Mb and contains 10 genes including DYRK1A (Matsumoto et al., 1997). The identification of two unrelated patients with microcephaly carrying a DYRK1A truncated mutation in hemizygosis (see bellow; Moller et al., 2007) indicates that haploinsufficiency of DYRK1A is most likely the cause of the common features presented by these two patients and by patients with partial monosomy 21.



Map of the Chromosomal region in 21q22.13 - 21q22.2 where DYRK1A is located. Genes (in green) and predicted gene (in black) surrounding DYRK1A are depicted according to the chromosomal position in NCBI Map Viewer (version released in August 2009). Direction of the arrowhead indicates the orientation of the gene.



Schematic representation of the exon-intron organization of human DYRK1A gene. The size of introns and exons is in kb. Exons (boxes) are numbered and drawn to scale: in orange, coding exons; in blue, alternative first exons. The position of major transcription start sites (TSSs) according to Maenz et al. (2008) is indicated with blue arrows. Alternative splicing events are shown with dotted lines and numbered from a-e.

DNA/RNA

Description

The DYRK1A gene contains at least 12 exons spanning approximately 149.7 kb of genomic DNA.

Transcription

Several transcripts have been identified as result of alternative splicing (Wang et al., 1998; Guimerá et al., 1999; Maenz et al., 2008). The use of two alternative first exons, controlled by different promoter sequences, does not affect the open reading frame (alternative splicing events a and b). These two promoters differ in their strength and regulation by the transcription factor E2F1 (Maenz et al., 2008). Exclusion of exon 2 would give rise to a N-terminal truncated protein (alternative splicing event c). The use of an alternative acceptor site within exon 4 (alternative splicing events d and e) generates two protein variants that differ by the inclusion/exclusion of 9 amino acids in the N-terminal region (Kentrup et al., 1996; Guimerá et al., 1999). No functional differences have been associated to any of these variants. Further splice variants, affecting the C-terminal region, were identified by PCR cloning (Guimerá et al., 1999), although the existence of the protein isoforms encoded by these transcripts has not yet been confirmed.

Pseudogene

No pseudogene reported.

Protein

Description

The DYRK1A gene encodes two main protein isoforms of 763 and 754 amino acids. DYRK1A is a protein kinase that belongs to the DYRK family of dual-specificity protein kinases (CMGC group: DYRK family: DYRK subfamily). The kinase domain is located centrally in the primary structure of the protein. DYRK1A shares with the other DYRKs a conserved motif N-terminal to the kinase domain known as DYRK homology (DH)-box. It also harbors a functional, bipartite nuclear localization signal (NLS) N-terminal to the DH-box, a second NLS between subdomains X and XI within the kinase domain, a C-terminal PEST motif, and a polyhistidine tract that acts as a nuclear speckle targeting signal. When analyzed by Western blot with antibodies raised against the C-terminal, the protein appears as three bands around 90 kDa.

Expression

At the RNA level, DYRK1A is expressed as an approximately 6 kb transcript in many fetal and adult tissues including brain, heart, lung and skeletal muscle (Guimerá et al., 1996; Shindoh et al., 1996; Song et al., 1996). At the protein level, human DYRK1A expression has been mainly studied in the central nervous system, where it is detected in cortex, hippocampus, amygdala, thalamus and substantia nigra (Wegiel et al., 2004). The number of DYRK1A immunopositive neurons increases with maturation of human brain and an increase in the number of DYRK1A-positive astrocytes in aged people has also been observed (Weigel et al., 2004). Work done in mice has led to the proposal that Dyrk1a is expressed in sequential phases of central nervous system development; i) scattered expression in individual pre-neurogenic progenitors; ii) throughout the cell cycle in neurogenic progenitors; ii) down-regulated in post-mitotic neurons as they migrate radially; and iv) sustained expression in late differentiating neurons (Hammerle et al., 2008). Based on these observations, DYRK1A has been suggested to be critical for the coupling of the sequential events required for proper neuronal development.

The analysis of the human DYRK1A promoter found two promoter regions that respond differentially to the cell cycle-related transcription factor E2F1 (Maenz et al., 2008). Binding of the AP4-geminin complex to the human DYRK1A promoter has been shown by chromatin immunoprecipitation assays; moreover, the DYRK1A promoter is downregulated by AP4 overexpression in gene reporter assays, suggesting that the AP4-geminin repressor complex could be responsible of the DYRK1A downregulation in non-neuronal cells (Kim et al., 2004). In mice, Dyrk1a is transcriptionally induced by the receptor activator of nuclear factor kappa-B ligand (RANKL) cytokine through the activity of the nuclear factor of activated T-cells (NFAT) transcription factors (Lee et al., 2009).

Localisation

When overexpressed in mammalian cells, DYRK1A protein mainly localizes in the nucleus and shows a punctuated staining that it is

Schematic representation of DYRK1A protein. NLS: nuclear localization signal. DH: DYRK-homology box. PEST: Pest motif. His: Polyhistidine stretch. S/T: Serine and threonine-rich region. The line shows the alternatively spliced segment of 9 amino acids.

compatible with its accumulation in nuclear speckles (or splicing factor compartment) (Becker et al., 1998; Alvarez et al., 2003). Two nuclear localization signals contribute to DYRK1A nuclear translocation and the histidine stretch is responsible for the accumulation of the protein in nuclear speckles (Alvarez et al., 2003). Endogenous DYRK1A is detected in both the nucleus and the cytosol of human neurons, but only in the cytosol of astrocytes (Wegiel et al., 2004). Within the cytosol, DYRK1A accumulates in the cell bodies, dendrites and synapses (Wegiel et al., 2004). Similar behaviour has been described for mouse and chicken Dyrk1a (Marti et al., 2003; Hammerle et al., 2003; Laguna et al., 2008). These findings also correlate with the observed nuclear-cytosolic partitioning of Dyrk1a in mouse brain by biochemical fractionation (Aranda et al., 2008).

In certain pathological situations like the neurodegeneration associated to sporadic Alzheimer's disease and Down syndrome, DYRK1A is detected in neurofibrillary tangles, in granules in granulovacuolar degeneration and in corpora amylacea (Wegiel et al., 2008).

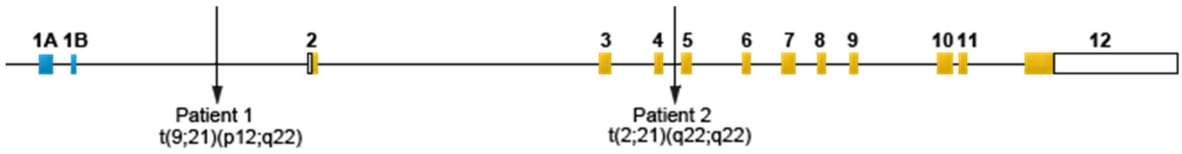
Function

DYRK1A is a dual-specificity protein kinase that autophosphorylates on tyrosine serine and threonine residues, but phosphorylate substrates only on serine or threonine residues. Autophosphorylation of Tyr 312/321 (754/763 variants) in the activation loop is required for full catalytic activity (Himpel et al., 2001; Lochhed et al., 2005). A full list of the residues phosphorylated in DYRK1A can be found at PhoSphositePlus. A consensus phosphorylation sequence has been proposed for DYRK1A (RPXS/TP) (Himpel et al., 2000), although some phosphorylation sites have been found that do not fit within the consensus such as in the case of LTAT(434)P in SF3B1/SAP155 or RPAS(640)V in glycogen synthase (Skurat et al., 2004; de Graaf et al., 2006).

The phenotypic analysis of a loss-of-function mouse model has provided information about DYRK1A functional roles. Null Dyrk1a embryos present a severe developmental delay and die around embryonic day 10.5, and the analysis of the heterozygous animals has indicated that DYRK1A plays a role in brain development (Fotaki et al., 2002). In this context, DYRK1A has been shown to participate in neuritogenesis (Benavides-Piccione et al., 2005; Gockler et al., 2009; Lepagnol-Bestel et al., 2009; Scales et al., 2009), and DYRK1A overexpression potentiates nerve growth factor (NGF)-mediated neuronal differentiation in PC12 cells through an enhancement of Ras/MAPK signalling (Kelly and Ramahni, 2005) or exit from the cell cycle in neuronal progenitors (Park et al., 2010; Yabut et al., 2010). Furthermore, an increase in DYRK1A gene dosage alters the levels of neuron-restrictive silencer factor (NRSF or REST), a key regulator of neuronal differentiation (Canzonetta et al., 2008). In the adult brain, DYRK1A regulates epidermal growth factor (EGF) signalling in stem cell daughters and reduced levels of DYRK1A compromise stem cell longevity (Ferron et al., 2010). These evidences together with DYRK1A overexpression in Down syndrome individuals (Dowjat et al., 2007) and the phenotype of mouse models of overexpression (Smith et al., 1997; Altafaj et al., 2001; Ahn et al., 2006), have led to the proposal of DYRK1A as a main contributor to Down syndrome neurological alterations (reviewed in Park et al., 2009a). Finally, there are increasing evidences of a link of DYRK1A with neurodegeneration, given that it phosphorylates several proteins related to this cellular process including tau, alpha-synuclein, septin-4, presenilin or amyloid beta precursor protein (APP) and accumulates in amyloid lesions (reviewed in Park et al., 2009b).

Additionally, the participation of DYRK1A in different cellular processes and signal transduction pathways has been inferred from the activity of its interactors and substrates. Functional activities include apoptosis, exerting a protective role through phosphorylation of caspase-9 or the deactelylase sirtuin-1 (SIRT1) (Seifert et al., 2008; Laguna et al., 2008; Guo et al., 2010); endocytosis, through the interaction and phosphorylation of the GTPase dynamin-1, the phosphatase synaptojanin-1 or the scaffold protein amphiphysin-1 (Murakami et al., 2009; and references therein); cytoskeletal-related processes, through phosphorylation of tau or microtubule-associated protein 1B (MAP1B) (Woods et al., 2001; Scales et al., 2009); receptor tyrosine kinase-dependent signalling, through the interaction with the kinase B-Raf (NGF) or the inhibitor Sprouty-2 (FGF) (Kelly and Rahmani, 2005; Aranda et al., 2008).

A relevant group of DYRK1A substrates are chromatin regulators and transcription factors suggesting a role for DYRK1A in the regulation of gene expression programs. When assayed in gene reporter assays, DYRK1A works as an activator of cAMP responsive element binding protein 1



Schematic representation of DYRK1A gene indicating the location of the breakpoints in chromosome 21 (vertical arrows) of the reported patients with a de novo balanced translocation.

(CREB1) (Yang et al., 2001), Gli1 (Mao et al., 2002), forkhead box protein O1 (FOXO1/FKHR) (von Groote-Bidlingmaier et al., 2003) or androgen receptor-interacting protein 4 (ARIP4/RAD54L2) (Sitz et al., 2004) and as an inhibitor of Notch-dependent transcription (Fernandez-Martinez et al., 2009). DYRK1A acts as negative regulator of NFAT transcription factors in distinct cellular environments by inducing their translocation to the cytosol (Arron et al., 2006; Kuhn et al., 2009; Lee et al., 2009). DYRK1A cooperation with glycogen synthase kinase 3 (GSK3) promotes the degradation of cryptochrome 2 (CRY2), thus contributing to the internal cellular clock (Kurabayashi et al., 2010). Another DYRK1A target is the tumour protein p53, either by being a direct DYRK1A substrate or indirectly through the phosphorylation by DYRK1A of the p53 deactelylase SIRT1 (Guo et al., 2010; Park et al., 2010). Finally, DYRK1A has been proposed as a regulator of splicing based on DYRK1A localization in nuclear speckles (Alvarez et al., 2003) and on having several splicing factors such SF3b1 or ASF as substrates (de Graaf et al., 2006; Shi et al., 2008). In fact, DYRK1A phosphorylation of the alternative splicing factor ASF prevents ASF-mediated inclusion of the alternatively spliced exon 10 in tau mRNA (Shi et al., 2008).

Homology

Mouse and human DYRK1A show a high degree of homology at the amino acid level (99%). The Drosophila DYRK1A orthologue is the minibrain gene (Tejedor et al., 1995). Within the DYRK family of kinases, the closest paralogous is DYRK1B.

Mutations

Note

A truncated mutation in DYRK1A gene has been identified in two unrelated patients that present prenatal onset of microcephaly, intrauterine growth retardation, developmental delay, severe feeding problems and febrile seizures. In both patients, truncation of DYRK1A results from a de novo balanced translocation involving chromosome 21, t(9;21)(p12;q22) in one patient and t(2;21)(q22;q22) in the other (Moller et al., 2008). Location of the breakpoints within DYRK1A is depicted in the diagram above.

Implicated in

Various types of cancer and disease

Disease

There are evidences suggesting a role of DYRK1A in several human diseases. All the evidences, with the exception of those reported in Moller et al. (2008) regarding microcephaly, are based on in vitro molecular and biochemical studies, on RNA expression studies and on studies in model organisms, mainly in the mouse. The list of human diseases includes Down syndrome (reviewed in Hammerle et al., 2003; Park et al., 2009a), early onset microcephaly (Moller et al., 2008), Alzheimer and Huntington diseases (reviewed in Park et al., 2009b), several cancer types (Baek et al., 2009; de Wit et al., 2002) and cardiac hypertrophy (Khun at al., 2009; Raaf et al., 2009).

Oncogenesis

Experiments performed in the Ts65Dn trisomic mouse model for Down syndrome have shown that overexpression of DYRK1A contributes to the attenuation of the calcineurin pathway induced by the increased dosage of RCAN1 (also named DSCR1), a chromosome 21 gene that like DYRK1A is triplicated in this model (Baek et al., 2009). The reduction in calcineurin signalling leads to a significant reduction of angiogenesis and tumour growth. Because the incidence of many cancer types is significantly reduced in people with Down syndrome (complete trisomy of chromosome 21), the results obtained in mice suggest that small differences in the amount of DYRK1A kinase could, through the calcineurin-dependent regulation of angiogenesis, modify the growth of some type of tumours also in humans (Pussegoda et al., 2010). By contrary, phosphorylation of caspase-9 by DYRK1A may have a negative role in cancer because a reduction of caspase-9 apoptotic activity protects mitotic cells from apoptosis and promotes cell survival during tumorigenesis (Allan and Clarke, 2007).

DYRK1A has been shown to interact with two viral oncoproteins, adenovirus E1A and human papilloma virus (HPV) E7 (Zhang et al., 2001; Liang et al., 2008; Komorek et al., 2010), which could be suggestive of the involvement of DYRK1A in oncogenic transformation.

Melanoma

Note

DYRK1A mRNA levels in a melanoma cell line with high metastatic potential (Mel57) are lower than in a melanoma cell line (1F6) with poor metastatic potential. DYRK1A mRNA levels are down-regulated in vivo during melanocytic tumour progression, and in tumour samples from lung, oesophagus, colon, pancreas and testis when compared to normal samples from the same tissues (de Wit et al., 2002).

Cervical cancer

Note

HPV type 16 (HPV16) is a tumorigenic virus that causes the development of cervical cancer. DYRK1A is present in HPV16 immortalized keratinocytes but not in primary keratynocytes; moreover, malignant cervical lesions contain more DYRK1A than normal tissue (Chang et al., 2007). Biochemical data lead to the suggestion that the increased expression of DYRK1A in immortalized keratinocytes and in cervical tissues acts as an antiapoptotic factor in the FKHR-dependent pathway leading to tumour development (Chang et al., 2007). Additionally, DYRK1A interacts and phosphorylates the HPV16 protein E7 leading to its stabilization and to an increase in its capacity for forming clones in a colony-formation assay (Liang et al., 2008).

Pancreatic endocrine neoplasms

Note

Microarray hybridization data showed up-regulation of DYRK1A in metastatic pancreatic endocrine neoplasms when compared with nonmetastatic pancreatic endocrine neoplasms (Hansel et al., 2004).

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