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Gene Section
Short Communication

VRK2 (vaccinia related kinase 2)

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Identity

HGNC (Hugo): VRK2

Location: 2p16.1

Local order: Telomere -- LOC100131953 - VRK2 - FANCL - EIF3FP3 -- Centromere.

Note:

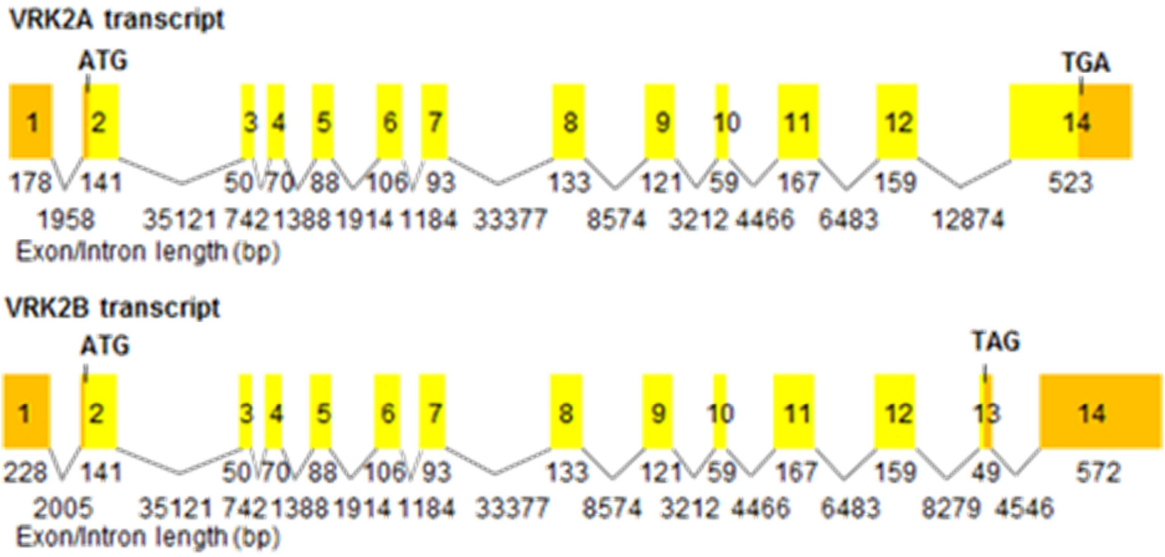
Member of the kinase branch in the human kinome (Manning et al., 2002) that separated into the Vaccinia-related kinase subfamily and the Casein kinase 1 serine/threonine protein kinase family (Nezu et al., 1997; Nichols and Traktman, 2004).

DNA/RNA

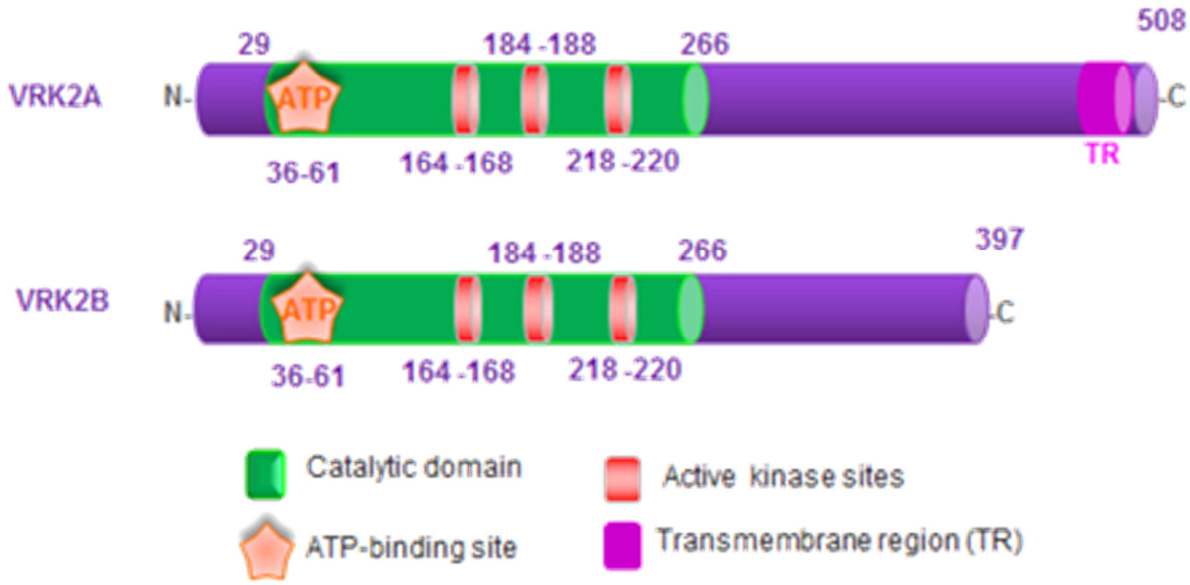
The subcellular localization of protein codified from this gene is dependent on two alternatively spliced variants (Blanco et al., 2006). Other alternative splicing messages have been detected but no proteins have been identified expressed from these alternative messages in humans.

Description

According to Entrez-Gene, VRK2 gene maps to NC_000002.11 in the region between 58273777 and 58387055 on the plus strand and spans across 113.180 kilobases.



VRK2 gene structure based in data available in Ensembl release 66. Two alternatively spliced variants coding two isoforms, VRK2A and VRK2B. Non-coding regions of exons are indicated in orange and coding regions in yellow. Exon lenght is indicated in scale (and number of base pairs are indicated below). Exon number is indicated within the exon. Introns are not in scale and intron lenght is indicated below each intron.



Isoforms of human VRK2 protein. They share identical sequence until aminoacid 394.

Transcription

Initiation codon located in exon 2. Normal message is 1888 nucleotides and has 13 exons (isoform VRK2A). An alternatively spliced variant have been detected with a message of 2036 nucleotides and 14 exons (isoform VRK2B).

Pseudogene

None. There are two closely related genes: VRK1 and VRK3 (Nichols and Traktman, 2004).

Protein

Note

Enzyme number (IUBMB): EC 2.7.11.1.

Description

VRK2 protein has two isoforms: VRK2A isoform is a 508 amino acid 58.141 KDa protein and VRK2B isoform, a 397 amino acid 45.030 KDa protein (Blanco et al., 2006).

Both isoforms present a serine-threonine kinase domain (residues 29-266) with an ATP-binding site (residues 36-61) and three active kinase motifs (residues 164-168, 184-188 and 218-220). Protein autophosphorylated in several residues (Nichols and Traktman, 2004).

Expression

VRK2A is widely expressed in normal and tumoral cells and all human cell lines tested expressed this isoform. VRK2B is expressed only in some cell lines (Blanco et al., 2006; Fernandez et al., 2010). VRK2A expression positively correlated with estrogen and progesterone receptors and inversely with ErbB2 in breast carcinomas (Fernandez et al., 2010).

Localisation

VRK2A contains a hydrophobic domain in the C-terminal region that anchors this protein to reticulum endoplasmic and mitochondria membranes. VRK2B lacks this region and it is a soluble protein localized in cytosol and nucleus (Blanco et al., 2006).

Function

Serine-threonine kinase activity (Nichols and Traktman, 2004).

VRK2 modulates signals mediated by mitogen-activated protein kinases (MAPK).

Both isoforms interacts with JIP1 protein inhibiting the phosphorylation state of JNK and the AP-1 transcriptional responses mediated by IL-1 and hypoxia signals (Blanco et al., 2007; Blanco et al., 2008).

Also, VRK2A interacts with the anchorage protein KSR1 and Mek1 inhibiting Raf-Ras-Mek1-Erk1/2 signaling mediated by EGF (Fernandez et al., 2010).

VRK2A interacts with BHFR1 protein from Epstein-Barr virus (a homologue of human anti-apoptotic Bcl-2 protein) enhancing viral survival after infection (Li et al., 2006).

VRK2A and VRK2B phosphorylate p53 in T18 in vitro, but only VRK2B stabilizes and activates p53 in vivo (Blanco et al., 2006).

VRK2 activity is inhibited by the small GTPase RAN protein (Sanz-Garcia et al., 2008).

Homology

The kinase domain of VRK2 presents several differences to most of protein kinases. DFG and APE motifs, that limited activation loop, are substituted by DYG and SID motifs respectively.

VRK2 protein structure, as well as other VRK proteins, presents an additional helix (αC4) in the N-lobule that

anchors αC helix to the C-lobule (Scheeff et al., 2009).

Mutations

Note

Mutation reported in Catalogue of Somatic Mutations in Cancer from Sanger Institute.

Somatic

Ovarian carcinoma: heterozygous mutation in nucleotide 32 in the cDNA coding region; T to A (missense substitution, L11H).

Implicated in

Breast cancer

Note

Immunohistochemistry: There is a high expression of VRK2 protein in breast carcinomas positive for estrogen and/or progesterone receptors (Fernandez et al., 2010). Breast carcinomas expressing ERBB2 have low levels of VRK2 protein (Fernandez et al., 2010).

Oncogenesis

VRK2 is a negative modulator of MAPK pathway in response to EGF through interaction with the KSR1 scaffold protein. VRK2 inhibits activation of ERK in response to EGF, ERBB2, RAS^{G12V} and V600E ID: 50574>, without affecting the AKT pathway (Fernandez et al., 2010).

Adrenocortical carcinoma

Cytogenetics

Loss of heterozygosity/allelic imbalance in a minimal region flanked by D2S391 and D2S288 markers in 2p16, was observed associated with carcinomas but not with benign tumors (Kjellman et al., 1999).

Infertility

Disease

Vrk2 -/- and pog -/- mice are infertile due to no development of follicles in females and lack of spermatogenesis in males (Lu and Bishop, 2003).

Cortical dysplasia

Disease

VRK2 gene was suggested as a gene responsible to cortical dysplasia presented in several patients with a microdelection in the p15-16.1 region of chromosome 2 (Chabchoub et al., 2008). However, another study reported that VRK2 gene is not included in this critical region (Felix et al., 2010).

Schizophrenia

Disease

A novel variant, rs2312147[C], showing association with an increased risk of schizophrenia is located over 50 kb upstream of VRK2 gene in 2p15.1 region (Steinberg et al., 2011).

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