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Gene Section
Review

ATP2B4 (ATPase, Ca++ transporting, plasma membrane 4)

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Abstract

Review on ATP2B4, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: ATP2B2, MXRA1, PMCA4, PMCA4b, PMCA4x

HGNC (Hugo): ATP2B4

Location: 1q32.1

DNA/RNA

Description

The human ATP2B4 gene (ATPase, Ca++ transporting, plasma membrane 4) is coding subunit of plasma membrane Ca2+ ATPase (PMCA). The ATP2B4 gene is located on the plus strand and spans 117295 bps of genomic region (203626787 - 203744081). There are 22 exons and 2 transcript variants for ATP2B4 gene (figure 1). The size of transcript variant 1 and transcript variant 2 is 8920 nt and 8742 nt, respectively.

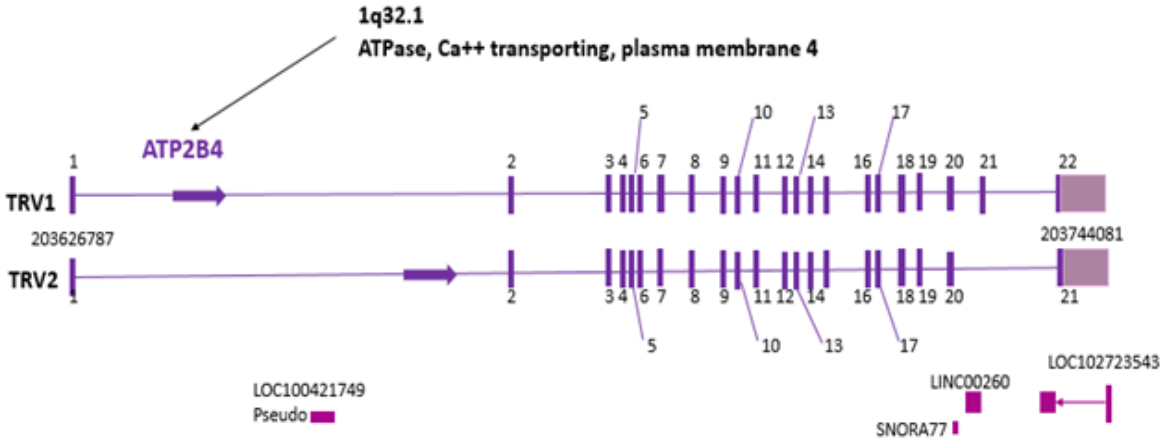

Figure 1. Location of ATP2B4 gene and representation of its transcripts. ATP2B4 is localized on chromosome 1q32.1 and consists of 2 transcript variant. Small RNA gene SNORA77, non-coding RNA LINC00260 and pseudogene LOC100421749 are encoded in this region.

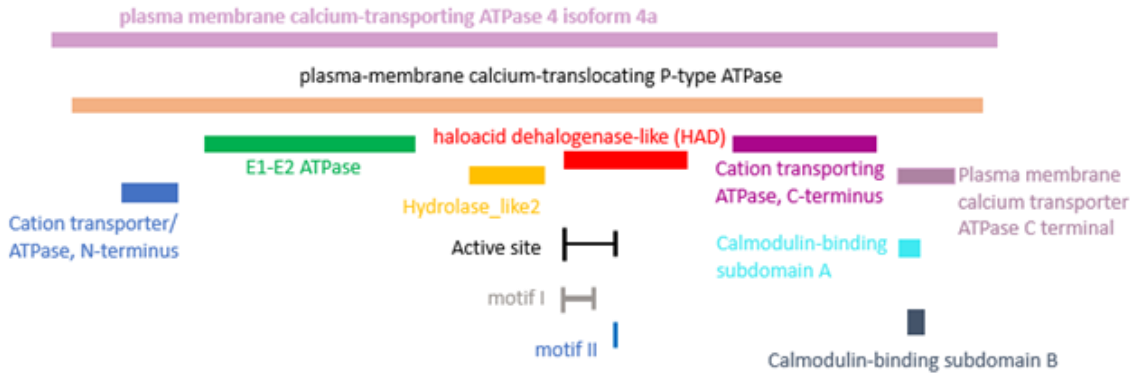

Figure 2. Figure showing different domains of ATP2B4 protein. Plasma-membrane calcium-translocating P-type ATPase (orange colored), E1-E2 ATPase (green colored), HAD_like (red coloures), cation transporting ATPase, C-terminus (purple coloured).

Transcript variant 1 represents the longer transcript and encodes the shorter isoform (4a). Plasma membrane calcium-transporting ATPase 4 isoform 4a (accession number NP_001001396.1) protein product comprise of 1170 amino acids (aa). Plasma membrane calcium-transporting ATPase 4 isoform 4b (accession number NP_001675.3) products of transcript variant 2 comprise of 1205 aa.

Transcription

ATP2B4 gene has 2 transcript variants. But Ensembl database shows 7 transcripts (splice variants). ATP2B4 mRNA transcript variant 1 (accession number NM_001001396.2) includes 22 exons and total annotated spliced exon length is 8920. It has 21 coding exons. Transcript variant 2 (accession number NM_001684.4) has 21 exons and 20 coding exons. It has total annotated spliced exon length 8742 (figure 1). ATP2B4 gene has an important role in maintaining intracellular calcium balance as it is involved in taking the calcium ions out of the cells. The extreme elevation of ATP2B4 gene expression during the differentiation of cells in colon cancer is thought to be associated with the calcium stream. Though not very clear with evidences, changes in expression levels of PMCA gene is shown as a distinctive feature of some colon cancer (Aung et al., 2007). An increase the expression of the ATP2B4 gene has been found in colorectal tumor patients (Geyik et al., 2014).

A pseudogene LOC100421749 is encoded in the intronic region of the ATP2B4 gene. At the same time, long intergenic non-protein coding RNA 260 (LINC00260), LOC102723543 and small nucleolar RNA, H/ACA box 77 (SNORA77) are also encoded by this gene. LINC00260 and SNORA77 are encoded in the same strand while LOC100421749 and LOC102723543 are encoded in the opposite strands (figure 1).

Pseudogene

There is no known pseudogene for ATP2B4.

Protein

Description

ATP2B4 protein is among one of the isoform of plasma membrane Ca2 + ATPase (PMCA). 4a and 4b are the two isoforms of this protein. Plasma membrane calcium-transporting ATPase 4 isoform 4a is encoded by transcript variant 1 and comprise of 1170 aa. Its molecular weight is 129.4 kDa with an isoelectric point of 7.4995. Plasma membrane calcium-transporting ATPase 4 isoform 4b comprising of 1205 aa is encoded by transcript variant 2. The molecular weight of this isoform is about 134 kDa and its isoelectric point is 6.3516.

Different regions like ATP2B4 protein, cation transporter/ATPase, N-terminus, plasma-membrane calcium-translocating P-type ATPase, E1-E2 ATPase, haloacid dehalogenase-like hydrolases; HAD_like domain, Putative hydrolase of sodium-potassium ATPase alpha subunit; HAD_like II domain and cation transporting ATPase, C-terminus are formed from plasma membrane calcium transporter ATPase C terminal domain (figure 2). Isoform 4a includes both calmodulin binding subdomain A and calmodulin binding subdomain B. But isoform 4b does not include these domains (figure 2).

Calcium ions are involved in the regulation of several cellular processes, including activation or inactivation of the cellular signaling pathways like calcium regulatory proteins (Berridge et al., 2003). Active transport of calcium ions in the plasma membrane which requires ATP hydrolysis is achieved through calcium pump (Monteith et al., 2007). P-type ATPase is responsible for translocating the extracellular calcium ions in eukaryotes. There are several isoforms of PMCA in human and mouse but without any additional functions. There are many diseases in humans which are supposed to be caused by errors in PMCA.

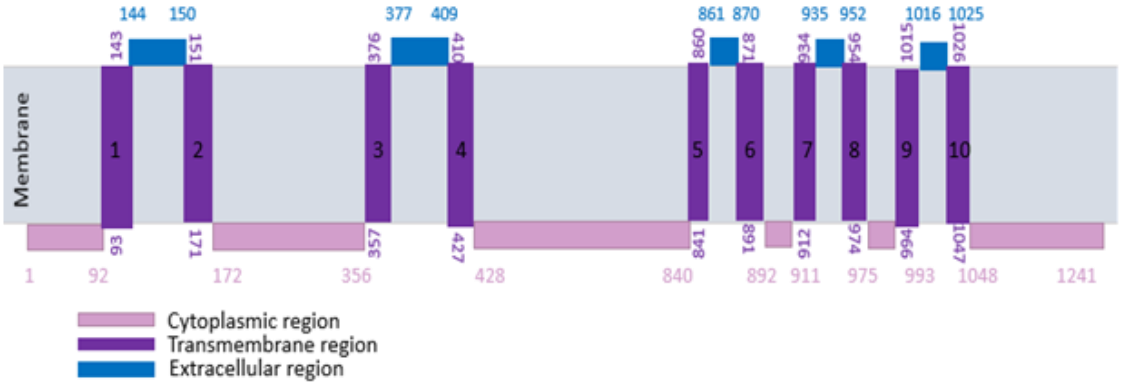

Figure3. Figure showing cytoplasmic region of plasma membrane of ATP2B4 protein. Localization of transmembranes and extracellular regions are shown. Ten transmembrane domains are also cited.

P-type ATPase in the plasma membrane calcium ATPase (PMCA) plays an important role in determining the amount of intracellular calcium (Jensen et al., 2004). Both N and C terminal of the calcium pump are located inside cells and contain 10 transmembrane regions. The C terminal is typically 70-200 aa in length and is considered to take part in the regulation of the calcium pump. Furthermore calcium ions are also responsible for stimulating tasks inside cells and this stimulus is generally provided by the calmodulin residing in the C terminal. Calmodulin is a calcium binding protein and is activated by its binding to calcium. Moreover, there are 4 isoforms and more than 30 alternative variants known for PMCA (Strehler and Zacharias, 2001). PMCA1 (ATP2B1) and PMCA4 (ATP2B4) were found in many cell types while PMCA2 (ATP2B2) and PMCA3 (ATP2B3) is reported to exist in different tissues (Carafoli, 1991; Strehler and Zacharias, 2001).

Expression

The expression of ATP2B4 protein varies according to the type of cancer. For example; ATP2B4 was found to be upregulated in the breast cancer cell lines (Varga et al., 2014). An increase the protein levels of ATP2B4 have been reported in the gastric cancer cell line (KATO-III) (Ribiczey et al., 2007). In another study with colon cancer, ATP2B4 protein expression from PMCA was found to be upregulated (Aung et al., 2007).

Localisation

ATP2B4 protein is localized in the plasma membrane. There are 10 transmembrane domains of this protein (figure 3). Cytoplasmic region, transmembrane region and extracellular regions of ATP2B4 are shown in figure 3.

Function

As shown in the structural form as well, ATP2B4 protein has role in the ATP binding as well as calmodulin binding activities. Calmodulin gets activated after binding to calcium ions and eventually activates the stimulating tasks of these ions. ATP2B4 is located in the tail of the C-terminal end (Brini et al., 2013).

Plasma membrane Ca2 + ATPases are dependent on ATP and are involved in the removal of calcium from the cell and thus are classified as transporter proteins in plasma membrane. These proteins have an important role in determining the amount of intracellular calcium (Jensen et al., 2004). The short term increase of intracellular Ca^{2+} in specific locations play a major role in muscle contraction and stimulus transduction pathways (Monteith et al., 2007; Roberts-Thomson et al., 2010).

Acidic phospholipids particularly polyphosphoinositides are strong stimulants of PMCA. As PMCA isoforms increase the access of phospholipids to acidic phospholipid binding sites, it effects the regulation of phospholipids (Strehler and Zacharias, 2001).

In a study related to ATP2B4 protein, it has been found that several members of MAGUK (membrane-associated guanylate kinase) protein show high interaction with PZD domains. This interaction was shown to take place due to the C terminal sequence (Kim et al., 1998). In another study, interaction of ATP2B4 with NOS-II has been shown in HEK293 cells. The interaction of NOS-I with PZD domain has also been shown (Schuh et al., 2001). The dose dependent inactivation of NOS-I has been shown to be mediated by ATP2B4 (Schuh et al., 2001).

ATP2B4 protein was found to be expressed in heart (Strehler and Zacharias, 2001). An interaction of nNOS with ATP2B4 proteins have been shown in cardiomyocytes. It also has been found to be overexpressed in cardiomyocytes (Williams et al., 2006).

ATP2B4 protein has two isoforms i.e 4a and 4b. 4b isoform showed low basal activity in the absence of calmodulin. This isoform is also slowly activated by Ca2+-calmodulin complex. The calmodulin-

activated pump is slowly inactivated in 4b isoform (Caride et al., 2001a; Caride et al., 2001b; Penheiter et al., 2002).
The full PMCA4b isoform as well as the C-terminally truncated PMCA4a splice variant is coded by PMCA4. Biochemically, PMCA4b has several distinguishing features: first, it shows low basal activity when there is no calmodulin; second, it gets slowly activated by the Ca2+-calmodulin complex; and third it slowly inactivates the calmodulin-activated pump (Caride et al., 2001a; Caride et al., 2001b; Penheiter et al., 2002).

Homology

ATP2B4 gene and domains of its protein have been found to be partially conserved in some animals. For example, the DNA sequence in P. troglodytes shows 99.6% similarity to humans and protein shows 99.9% similarity, the DNA sequence in M.musculus shows 84.1% similarity and protein shows 84.1% similarity. In S. pombe (ATP2B4 gene name; SPAPB2B4.04c), there is 50% DNA similarity and 44.8% protein similarity (data from NCBI BLAST).

Mutations

Somatic

6 somatic mutations have been identified in ATP2B4 gene.
1- NM_001001396.2(ATP2B4):c.-464-21082A>G: there is conversion of A>G at the region located 203661660 (GRCh38) of ATP2B4 gene. This mutation has been associated with lung cancer.
2- NM_001001396.2(ATP2B4):c.2027C>T (p.Pro676Leu): a missense mutation has been identified at the region located 203711104 of this gene. There is transformation of proline to leucine with conversion of C>T at 676 position. It is associated with malignant melanoma.
3- NM_001001396.2(ATP2B4):c.466C>T (p.Leu156Phe): a missense mutation has been identified at the region located 203699534 of this gene. There is transformation of leucine to phenylalanine at position 156 with conversion of C>T at 466 position. It is also associated with malignant melanoma.
4- NM_001001396.2(ATP2B4):c.760C>T (p.Pro254Ser): a missense mutation has been identified at the region located 203700316 of this gene. It is associated with malignant melanoma. There is transformation of proline to serine with conversion of C>T at 760 position.
5- NM_001001396.2(ATP2B4):c.2799C>T (p.Ile933=): there is no change in the amino acid sequence with C>T transformation at region located at 203721397. Isoleucine remains isoleucine even after C>T transformation at 933 position. This type of mutation is termed as synonymous or silent mutations.
6- GRCh38/hg38 1q31.1-42.11(chr1:187143981-224299417)x3: this mutation location is Chr1:187143981 - 224299417 (on Assembly GRCh38). Copy number gain variant has been found at a cytogenetic location 1q31-42.1 (Kaminsky et al., 2011). ATP2B4 gene is also localized at this region. It belongs to pathogenic allele class.

Implicated in

Colorectal cancer

Prognosis
ATP2B4 mRNA levels have been shown to reduce in a significant way in adenocarcinoma and benign colon tumors as compared to normal colon tissue. In spite of increased ATP2B4 expression levels in differentiated colon cancer cells, decreased expression of levels of ATP2B4 in some colon cancers supports it to be their characteristic feature (Roberts-Thomson et al., 2010). In our previous study involving normal and tumor tissues of colorectal cancer patients, increased expression of ATP2B4 has been shown. Furthermore, ATP2B4 mRNA level in rectal cancer patients was found to be significantly increased when they were separately studied (Geyik et al., 2014). It is believed that ATP2B4 plays an important and specific role tumorigenesis of colon cells and colon cancer (Aung et al., 2007; Aung et al., 2009).

Gastric cancer

Prognosis
KATO-III, a gastric cancer cell line was treated with short chain fatty acids (SCFAs), Na+-valerate or Na+-butyrate. Na+-valerate and Na+-butyrate are well known differentiating agents and butyrate are physiologically located in the intestinal lumen (Ribiczey et al., 2007). ATP2B4 was found to be upregulated in KATO III cancer cell line after treatment with SCFAs. Both mRNA and protein level of ATP2B4 was to be significantly increased in gastric cancer cell line (Ribiczey et al., 2007).

Breast cancer

Prognosis
ATP2B4 was found to be overexpressed in breast cancer. The expression level of ATP2B4 was studied in some breast cancer cell lines like MCF-7, MDA-MB-231, and MCF-10A according to their confluence and subconfluence states. However, a significant difference was not found (Lee et al., 2005). However, ATP2B4 mRNA level was found to be significantly lower in tumorigenic cell lines (ZR-75-1, T-47D, BT-483, and SK-BR-3) as compared to non-tumorigenic breast epithelial cell lines (184A1 and 184B5) (Lee et al., 2005). The breast cancer cell MCF-7 cells were treated with SCFAs like butyrate, phenylbutyrate, and valerate. ATP2B4 protein level was found to increase after

this treatment. The remodeling of Ca2 + homeostasis in cancer cells is a distinguishing feature of tumor progression and the role of ATP2B4 during this process has been supported by many studies (Varga et al., 2014).

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