Gene Section
Review

PFKFB2 (6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2)

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Abstract

Review on PFKFB2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: PFK-2/FBPase-2

HGNC (Hugo): PFKFB2

Location: 1q32.2

Local order

The human PFKFB2 gene is located on the chromosome 1 at position 1q31-q32.2 (GeneCards) (Fig. 1).

DNA/RNA

Description

The human PFKFB2 is composed of 15 exons spanning 22617 bp (GenBank: AJ005577.1). This gene has 9 transcripts; two of them have been reported to codify a protein and three contain an open reading frame, but no protein has been identified. The transcripts are derived from different promoters and vary only in non-coding sequences at the 5' end. Therefore, the resulting proteins differ in their C-terminal amino acid sequence (Heine-Suñer et al., 1998).

The main products of the gene correspond to mRNAs of 7073 bp and 3529 bp for the variant 1 (isoform a; NM_006212.2) and variant 2 (isoform b; NM_001018053.1), respectively (Fig. 2). The isoform b differs in the 3' UTR and the coding region compared to isoform a. The resulting isoform b is shorter and has a distinct C-terminus compared to isoform a. However, it is not known how these different 5' ends are related to the three mRNAs (H1, H2 and H4) that encode the isoform a or the H3 mRNA that encodes the isoform b. None of these mRNAs are strictly heart-specific.
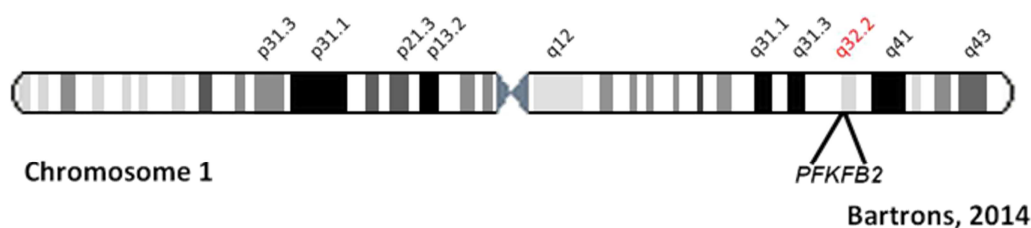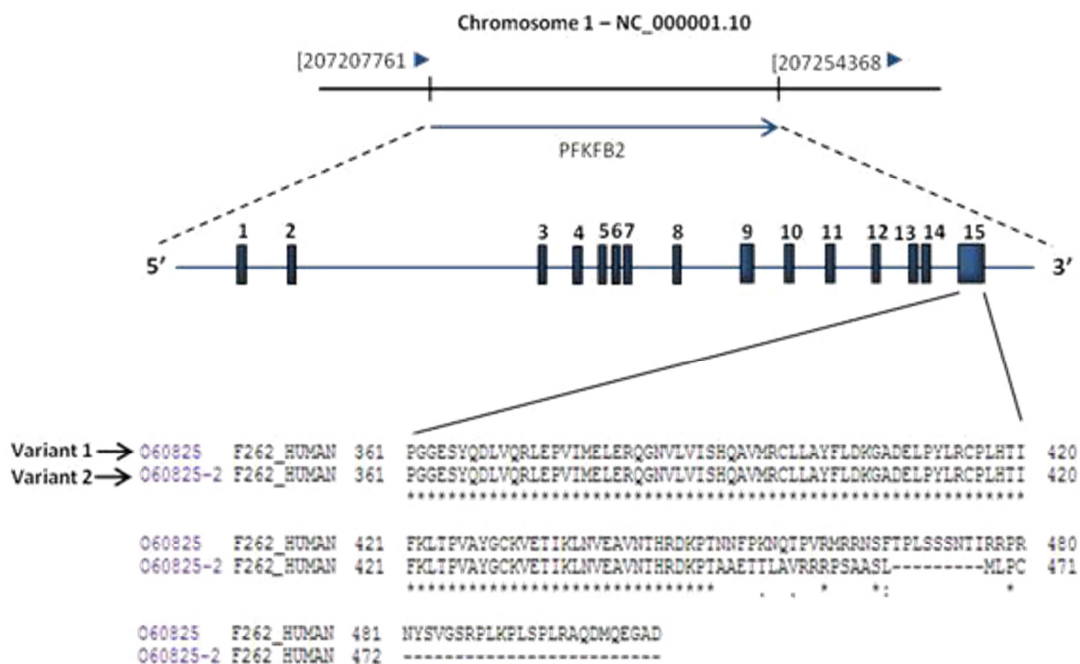

Figure 1. Localization of human PFKFB2 gene.

Figure 2. Schematic representation of the location of PFKFB2 gene in chromosome 1 and its structural organization. Description of the exon/intron splice junctions. Exon sequences are shown in vertical bars numbered 1-15. The sequences of 060825 and 060825-2 correspond to variant 1 and variant 2, respectively (NCBI).

The overall gene structure of the human PFKFB2 gene has exons clustered into three groups. The first group contains exons 1 and 2 that are different from those in other PFKFB2 genes and contain the ATG initiation codon in exon 2. The second group contains exons 3-8 coding for the PFK-2 domain and the third group contains exons 8-15 coding for the FBPase-2 domain and a carboxy-terminal regulatory domain. Gene structure, exon-intron organization, as well as intron sizes, are similar to those of the rat and bovine homologous genes.

Transcription

The human PFKFB2 coding sequence consists of 1518 bp for isoform a and 1416 bp for isoform b from the start codon to the stop codon, although the immature transcript forms contain 7904 bp and 3494 bp, respectively. Multiple alternatively spliced transcript variants have been described for this gene (Ensembl: OTTHUMG00000036033).

Pseudogene

No pseudogene of PFKFB2 is known.

Protein

Description

PFKFB2 is a homodimeric protein of 505 amino acids for isoform a and 471 for isoform b with a deduced molecular mass of 58 kDa and 54 kDa, respectively.

PFKFB2 is an enzyme of PFKFB family, as it shares different structure and function with the others isoenzymes.

PFKFB2 has two distinct catalytic sites in each subunit: one for the 6-phosphofruto-2-kinase (PFK-2) activity and the other for the fructose-2,6-bisphosphatase (FBPase-2) activity (El-Maghrabi et al., 1982; Pilkis et al., 1995; Okar et al., 2001).

The sequence of the catalytic core is highly conserved, whereas the N-terminal and C-terminal regions show more divergence (Rider et al., 2004).

PFK-2/FBPase-2 activities control fructose-2,6-bisphosphate (Fru-2,6-P$_2$) synthesis and degradation, regulating the rate of glucose metabolism.

More information about PFKFB2 protein can be found in Uniprot O60825.

Expression

PFKFB2 protein is expressed mainly in heart, although expression is also found in other tissues at lesser extent (Minchenko et al., 2002). Moreover, it is expressed in different cancer cell lines such as T-lymph Jurkat, K562 erythroleukemia, liver HepG2, lung A549, colon RKO, bone U2OS, brain GAMG, prostate LnCap, cervix HeLa and breast MCF7. All this information can be found in GeneCards (sections proteins and expression).

According to the RNAseq database, this gene can also be expressed in thyroid, brain, kidney, skeletal muscle, ovary, testis and others.
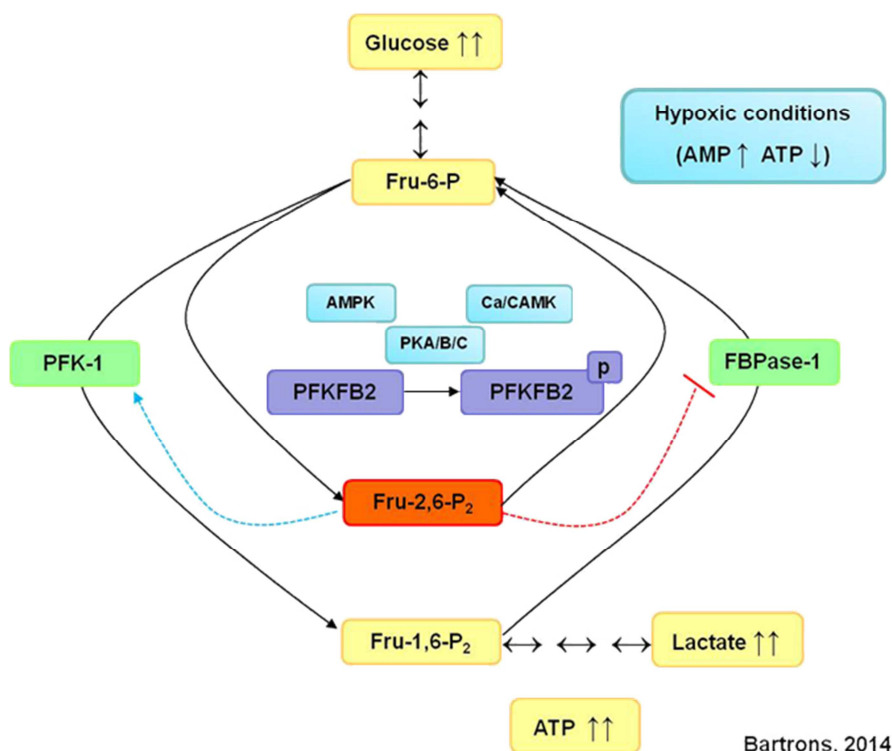
Figure 3. PFKFB2 activities and function in the glycolytic pathway in heart during hypoxia.

Localisation

PFKFB2 protein is active in the cytosol.

Function

This enzyme regulates the concentration of Fru-2,6-P_2 through the two catalytic domains. PFK-2 domain catalyzes the synthesis of Fru-2,6-P_2, using fructose-6-phosphate (Fru-6-P) and adenosine-5-triphosphate (ATP) as substrates; FBPase-2 domain catalyzes the degradation of Fru-2,6-P_2 into Fru-6-P and inorganic phosphate (Pi). These two mutually opposing catalytic activities are controlled by different mechanisms such that each activity is predominant in a given physiological condition. In detail, the reactions catalyzed are:

Kinase catalytic activity: ATP + D-fructose-6-phosphate $\Leftrightarrow$ ADP + beta-D-fructose-2,6-bisphosphate

Phosphatase catalytic activity: Beta-D-fructose-2,6-bisphosphate + H_2O $\Leftrightarrow$ D-fructose-6-phosphate + phosphate

The rate of glycolytic flux is controlled at different levels and by different mechanisms: substrate availability, enzyme concentrations, allosteric effectors and covalent modifications on regulatory enzymes. One of the critically modulated steps is that catalyzed by 6-phosphofructo-1-kinase (PFK-1), in which Fru-2,6-P_2 is the most powerful allosteric activator (Van Schaftingen, 1987; Okar and Lange, 1999; Rider et al., 2004). Fru-2,6-P_2 relieves ATP inhibition and acts synergistically

with adenosine monophosphate (AMP), inhibiting fructose 1,6-bisphosphatase (Fru-1,6-Pase) (Van Schaftingen, 1987). These properties confer to this metabolite a key role in the control of Fru-6-P/Fru-1,6-P_2 substrate cycle and hence critically regulates carbohydrate metabolism (Fig. 3).

In vertebrates, there are four different PFKFB genes (PFKFB1, PFKFB2, PFKFB3 and PFKFB4), which encode the PFK-2/FBPase-2 isoenzymes. Each of these enzymes has been originally identified in different mammalian tissues: PFKFB1 in liver and skeletal muscle, PFKFB2 in heart, PFKFB3 in brain, adipose tissue and proliferating cells, and PFKFB4 in testis (Okar et al., 2004; Rider et al., 2004). However, all four are widely expressed throughout the adult organism. These isoenzymes show differences in their distribution and kinetic properties in response to allosteric effectors, hormonal, and growth factors signals (Okar et al., 2001). PFKFB2 enzyme is overexpressed in different cancer cells like melanoma, prostate, pancreatic, gastric and mammary gland cells (Minchenko et al., 2005a; Minchenko et al., 2005b; Bobarykina et al., 2006). For more information about PFKFB genes see: PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3) and PFKFB4 (6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4).

Regulation

PFKFB2 is an essential enzyme for the regulation of glycolysis in heart. PFKFB2 is multisite-

phosphorylated, integrating signaling from many pathways via protein kinase cascades to a single molecule, Fru-2,6-P_2, to stimulate glycolysis.

The human PFKFB2 protein contains the Ser 29, Ser 466, Thr 475 and Ser 483 residues that regulate the activity of the enzyme. These residues are located in its C-terminal domain and can be phosphorylated by protein kinases such as AMPK, 3-phosphoinositide-dependent kinase-1 (PDK-1), cAMP-dependent protein kinase (protein kinase A; PKA), protein kinase B (PKB; also known as Akt), p70 ribosomal S6 kinase (S6K1), and mitogen-activated protein kinase 1 (MAPK-1). Phosphorylation of PFKFB2 results in the activation of the enzyme, increasing V_{max} of PFK-2 activity. The variations in PFK-2 activity, however, appear to be different with the phosphorylation by the different kinases (Marsin et al., 2000; Rider et al., 2004).

In perfused rat hearts, it has been shown that the concentration of Fru-2,6-P_2 is raised by increasing the work load, after hypoxia or stimulation with adrenalin or insulin (Hue et al., 1982; Rider and Hue, 1984; Depre et al., 1993; Deprez et al., 1997). This activation is probably mediated by the phosphorylation of three conserved residues (Ser 466, Thr 475 and Ser 483) by specific protein kinases (Depre et al., 1993; Deprez et al., 1997).

Insulin stimulates glycolysis in heart by a combination of an increase in glucose transport and activation of PFKFB2 (Depré et al., 1998; Hue et al., 2002). Two serine residues, Ser 466 ad Ser 483 can be phosphorylated in vitro by PKB in response to insulin resulting from a 2-fold increase in both Vmax and affinity for Fru-6-P, one of the substrates of PFK-2 (Lefebvre et al., 1996; Deprez et al., 1997).

Rat heart PFKFB2 is activated by insulin in vivo through a 2-fold increase in V_{max} with no change in K_m for Fru-6-P (Rider and Hue, 1984). Moreover, it has been shown that the insulin-induced activation of PFKFB2 was blocked by wortmannin, a PI3K inhibitor, but was insensitive to rapamycin or PD098059, which prevent the activation of p70^{S6K} and the MAPK cascade, respectively (Lefebvre et al., 1996). These results suggest that PI3K, but not p70^{S6K}, is involved in the activation of PFKFB2 in response to insulin. New in vitro and in vivo experiments show that SGK3 is not required for insulin-induced heart PFK-2 activation and this effect is likely mediated by PKBα (Mouton et al., 2010). Moreover, it has been proposed that 14-3-3s, that have been implicated in promoting cell survival (Masters et al., 2002), bind to PFK-2 at Ser 483 when it is phosphorylated by PKB in vitro in response to insulin or in cells that are stimulated with IGF-1 or transfected with active forms of PKB, mediating the stimulation of glycolysis by growth factors (Pozuelo et al., 2003).

Glycolysis in heart also increases in response to increased the workload (Depre et al., 1993; Beauloye et al., 2002), rising Fru-2.6-P_2 due to the activation of PFKFB2. The increase on workload activates PKB but not p70^{S6K} and this increase is blocked by wortmannin and is rapamycin-insensitive. Ca/CAMK (Ca^{2+}/calmodulin-activated protein kinase) is which phosphorylates and activates PFKFB2 secondarily to a rise in cytoplasmatic $Ca2^{2+}$ (Depre et al., 1993; Beauloye et al., 2002).

Adrenalin administration in perfused rat hearts suggests that PKA may be responsible for the activation of PFKFB2, which accounts for the increased Fru-2,6-P_2 levels (Narabayashi et al.,1985). This hormone promotes PFKFB2 phosphorylation by PKA in the residues already described in vitro, which are Ser 466 and Ser 483. These phosphorylations have an impact on PFK-2 activity, decreasing the K_m for Fru-6-P (Kitamura et al., 1988; Rider et al., 1992a; Rider et al., 1992b).

PFKFB2 mRNA is induced in organs exposed to hypoxic conditions. Activation of the AMP-activated protein kinase (AMPK) during ischemia or hypoxia leads to phosphorylation of PFKFB2 at Ser 466 which increases the levels of Fru-2,6-P_2 and stimulates glycolysis. PFKFB2 phosphorylation leads to an increase in V_{max} with no change in K_m for Fru-6-P (Marsin et al., 2000). Other studies have described PFKFB2 as a hypoxia-responsive gene in vivo but the regulation of its expression following hypoxic treatments appears to occur in a cell-specific manner. The mechanism underlying the expression of each isoform in different tissues remains unclear (Minchenko et al., 2002).

Moreover, amino acids increase the synthesis of Fru-2,6-P_2 in HeLa and MCF7 cell lines by phosphorylation at PFKFB2 at Ser 483. This activation is mediated by PI3K and PKB. Similar effects on Fru-2,6-P_2 metabolism were observed in freshly isolated rat cardiomyocytes treated with amino acids, which indicates that these effects are not restricted to human cancer cells. In these cardiomyocytes, PFKFB2 phosphorylation increases glucose consumption and the production of lactate and ATP (Novellasdemunt et al., 2013).

PFKFB2 is also a substrate of PKC which phosphorylates Ser 84, Ser 466 and Thr 475 (Rider and Hue, 1986; Kitamura et al., 1988; Rider et al., 1992a; Rider et al., 1992b). However, the physiological significance of phosphorylation of Ser 84, Ser 466 and Thr 475 of PFKFB2 by PKC is not completely understood. It seems that phosphorylation of Ser 466 or Thr 475 does not change the enzyme activity. This might be due to the fact that the phosphorylation at Ser 84 possibly counteracts the effects of phosphorylation at the activating C-terminal sites (Kitamura et al., 1988; Rider et al., 1992b).

The mechanism of control of PFKFB2 isoenzyme by phosphorylation is also difficult to explain in the absence of a crystal structure of the phosphorylated isoenzyme. Phosphorylation of Ser 466 and Ser 483 at the C-terminal end of the bovine heart isoenzyme by PKA (Kitamura et al., 1988; Rider et al., 1992a; Rider et al., 1992b; Deprez et al., 1997) and insulin-stimulated protein kinases (Deprez et al., 1997) activates PFK-2 by decreasing K_m for Fru-6-P and by increasing the V_{max} without affecting FBPase-2. Ser 466 phosphorylation is responsible for the increase in V_{max} whereas both phosphorylations are necessary to decrease the K_m for Fru-6-P (Bertrand et al., 1999).

Regulatory sequences that account for some of the mechanisms involved in the long-term hormonal control and tissue-specific expression of PFKFB2 have been identified. The 5' flanking sequence of PFKFB2 contains regions that are conserved between the human, bovine and rat genes. In these regions, several potential binding sites for the Sp1, HNF-1 and BHLH (helix-loop-helix) (E boxes) transcription factors and for the GR have been described (Tsuchiya and Uyeda, 1994; Chikri and Rousseau, 1995; Heine-Suñer et al., 1998), but a factor binding to these sites has not been reported.

Chromosomal rearrangements: copy number variants

There are three alterations affecting PFKFB2 genome region described in patients. One of them, the gain of 1:195266734-216326885, shows phenotypic effects such us visual impairment, low-set ears, iris coloboma, intellectual disability, defect in the atrial septum, ventricular septal defect and vertical nystagmus. For more information see DECIPHER.

No syndrome or disease was found in OMIM database.

Homology

Location in the mouse: chromosome 1, 56,89 cM, cytoband E4, 130689043-130729253 bp, complement strand (MGI).

For a comparison of the gene from Homo sapiens, mouse, rat, cattle, chimpanzee, chicken, zebrafish, rhesus macaque and dog see MGI.

Also for all species known gene tree, see Treefam database.

It appears that the use of Fru-2,6-P$_2$ as a regulatory metabolite is a specifically eukaryotic phenomenon. The most plausible hypothesis for the origin of the PFK-2/FBPase-2 would be the fusion of two ancestral genes coding for a kinase functional unit and a phosphohydrolase/mutase unit, respectively. From protein sequence alignments, it is clear that the bisphosphatase activity located in the C-terminal domain of the PFK-2/FBPase-2, the phosphoglycerate mutases (PGAMs) and the acid phosphatase family diverged from a common ancestor (Jedrzejas, 2000; Okar et al., 2001). Alignments of the bisphosphatase domain with PGM and acid phosphatase can be obtained at EBI. On the other hand, PFK-2 domain is related to a superfamily of mononucleotide binding proteins including adenylate kinase (AK) of E. coli., p21 Ras, EF-tu, the mitochondrial ATPase- β-subunits and myosin ATPase, all of them contain the Walker A and B motifs and have a similar fold (Rider et al., 2004).

Orthologs (from BLAST Local Alignment Tool)

Results from BLAST Local Alignment Tool are shown in Figure 5. Only the annotated proteins are reported, the predicted proteins appearing in the local alignment were excluded.
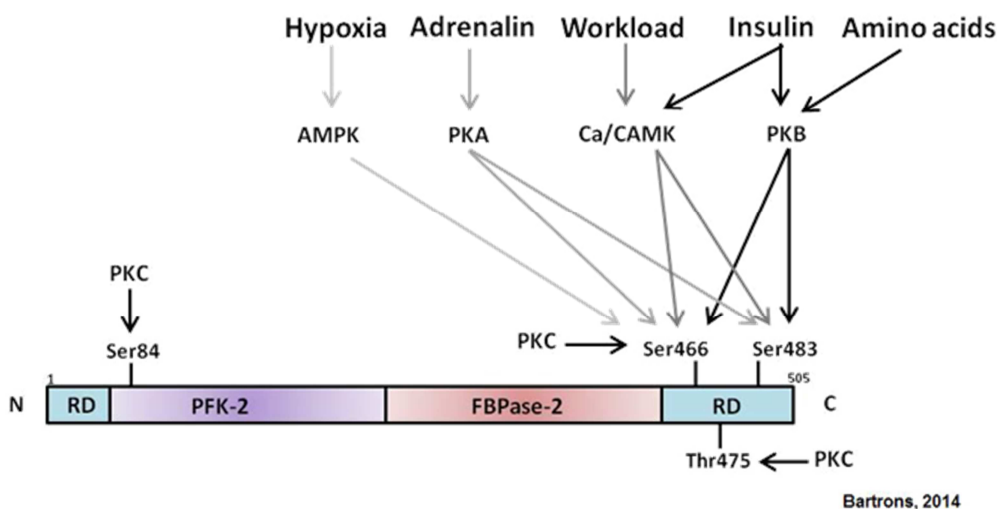

Figure 4. Domain organization and phosphorylation of PFKFB2 isoenzyme. The N-terminal PFK-2 domain is shown in violet, the C-terminal FBPase-2 domain is shown in red and the regulatory domains are shown in blue. Phosphorylation sites, the stimuli and the kinases responsible of their phosphorylation are indicated.

Specie	Gene	Query cover	E value	Identity
Pongo abelii	PFK/FBPase 2	99%	0.0	99%
Bos taurus	PFK/FBPase 2	100%	0.0	94%
Rattus norvegicus	PFK/FBPase 2 isoform a	97%	0.0	95%
Mus musculus	PFK/FBPase 2 isoform 1	99%	0.0	93%
Rattus norvegicus	PFK/FBPase 2 isoform b	97%	0.0	95%
Pan trogoldytes	PFK/FBPase 2	89%	0.0	99%
Macaca mulatta	PFK/FBPase 2	89%	0.0	99%
Mus musculus	PFK/FBPase 2 isoform 3	99%	0.0	89%
Xenopus (Silurana) tropicalis	PFK/FBPase 2	95%	0.0	85%
Mus musculus	PFK/FBPase 2 isoform 2	88%	0.0	93%
Rattus norvegicus	PFK/FBPase 2 isoform c	88%	0.0	93%
Macaca fascicularis	LOC101865223 uncharacterized protein	82%	0.0	99%
Danio rerio	PFK/FBPase 2 isoform a	94%	0.0	78%

Figure 5. Orthologs for PFKFB2 gene from BLAST Local Alignment Tool.

Comparison of the PFKFB2 cDNA sequence with the bovine and rat 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK-2/FBPase-2) heart isoforms shows 87-90% nucleotide and 92-95% amino acid identity (Sakata and Uyeda, 1990; Darville et al., 1991).

Mutations

Note

Genomic variants

There are 647 SNP variants described in PFKFB2 (see GeneCards).

The most SNP are found in non coding regions: 418 are presented in introns, 3 in splice donor variant, 107 in 3' UTR and 25 variant within a half kb of the end of gene and others.

Furthermore, 61 SNP are presented with the coding regions. The most of them are missense (31 variants) and also synonymous variants (19 variants) and only one frameshift.

Somatic

49 somatic mutations in the PFKFB2 gene detected in patient tumor samples are collected in the COSMIC database.

Coding silent substitutions: 20, which represent 40.8% of the mutations described among all patients.

Two of them have been found in two patients: c.1008C>G (p.T336T) and c.1419G>A (p.S473S).

Nonsense substitutions: 1, located in c.1051C>T (p.R351*).

Missense substitutions: 23, which represent 46.9% of the mutations described among all patients.

Deletions frameshift: 1, located in c.1044delT (p.F348fs*66).

Insertion frameshift: 1, located in c.703_407insT (p.Q235fs*37).

Deletion inframe: 2, located in c.28_30delAAC (p.N12delN) and in in c.82_84delTGT (p.C28delC).

Unknown mutation: 2, one of them located in c.376-2A>T and the other in c.840+1G>A.

No synonymous substitutions or chromosomal fusions in PFKFB2 gene have been described in any tumor sample.
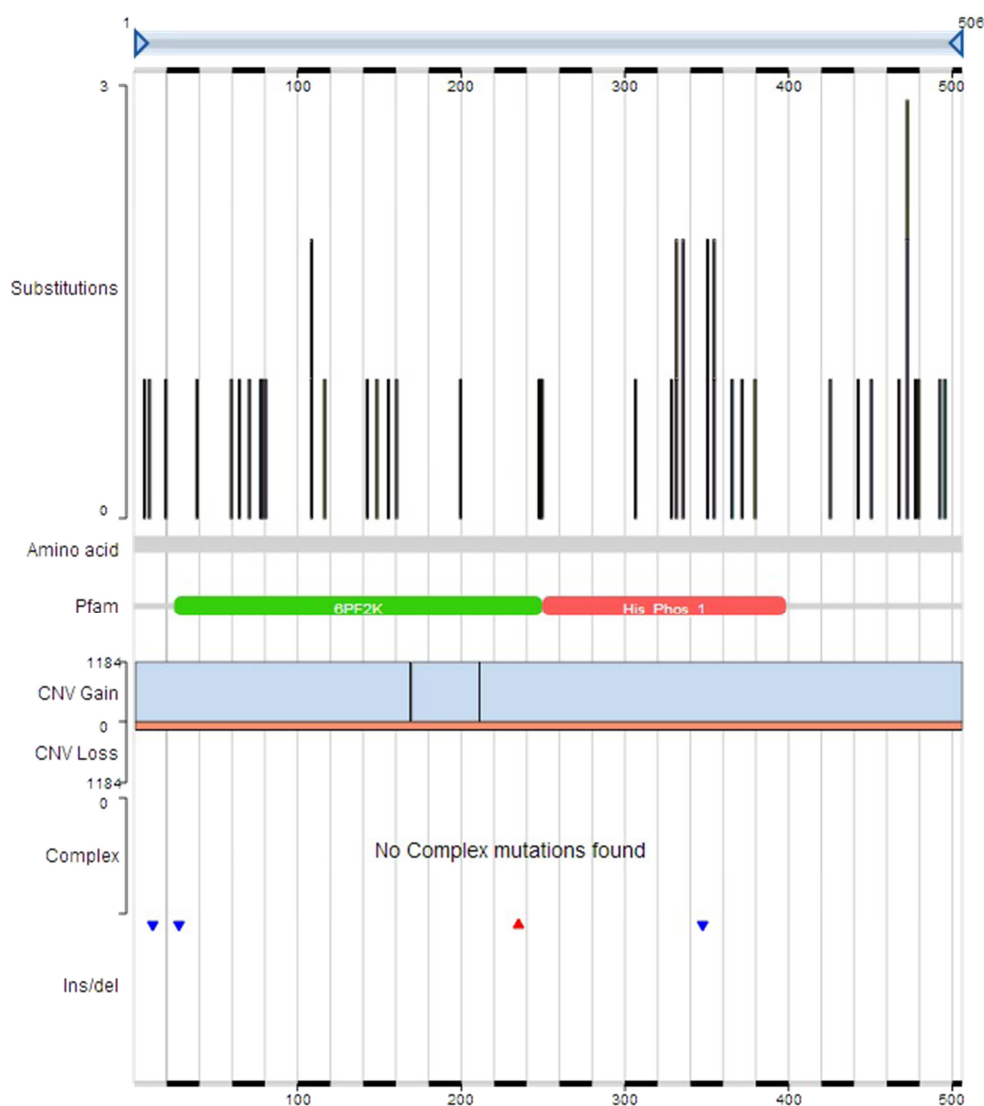
Figure 6. Histogram of mutations found among the amino acid sequence of PFKFB2 protein. The maximum number of substitutions at any specific genomic region is represented in Y axis. 6-phosphofructo-2-kinase and histidine phosphatase superfamily domains are represented in green and red respectively. From: COSMIC Database.

Implicated in

Various cancers

Oncogenesis

Cancer cells energy metabolism is characterized by a high glycolytic rate, which is maintained under aerobic conditions, when compared to non-malignant cells. The concentration of Fru-2,6-P_2 is generally increased due to overexpression and activation of PFK-2. Adrenaline, insulin, hypoxia and workload stimulate heart glycolysis by activating PFKFB2, hence producing a subsequent rise in Fru-2,6-P_2 concentration (Marsin et al., 2000; Rider et al., 2004).

Hypoxia is an important component of the tumor microenvironment. One key mediator of the hypoxic response in animal cells is the hypoxia-inducible factor (HIF) complex, a transcription factor frequently deregulated in cancer cells that induces the expression of glycolytic genes (Bartrons and Caro, 2007).

In culture cells, hypoxia induces PFKFB2 in HeLa and MCF7 cells. These data demonstrate that PFKFB2 is one of the responsive to hypoxia in vivo, indicating a physiological role in the adaptation of the organism to environmental or localized hypoxia/ischemia. Marsin et al. (2000) showed that AMPK phosphorylates PFKFB2 at Ser 466 in hypoxia conditions and this could contribute to maintain the high glycolytic rate that is a characteristic feature of many tumors.

Acute lymphoblastic leukemia

Note

Alterations in glucose metabolism have been implicated in cell death and survival decisions, particularly in the lymphoid lineage (Plas et al.,

2002) and in transformed cells (Tennant et al., 2010).

PFKFB2 was identified by microarray analysis of lymphoblasts isolated from glucocorticoid-treated children suffering from ALL (acute lymphoblastic leukemia) as one of the most promising candidate genes as a glucocorticoid (GC)-response gene, since it was regulated in the majority of patients. Its deregulation was proposed to entail disturbances in glucose metabolism which, in turn, have been implicated in cell death induction (Schmidt et al., 2006). These data suggest that cellular metabolism and apoptosis might be intertwined with connections between regulation of cellular bioenergetics and apoptosis. Carlet et al. (2010) demonstrated that both splice variants of PFKFB2 are expressed and specifically induced by GC in malignant lymphoid cells, however, functional analysis of this gene in the human T-ALL cell line model CCRF-CEM revealed that its over-expression does not explain the anti-leukemic effects of GC.

Prostate cancer

Note

In the early stages of prostate cancer, the androgen receptor (AR) is one of the key regulators that mediates tumor growth, promoting glucose uptake and anabolic metabolism, and modulates gene expression. Massie et al. (2011), using multiple metabolomic approaches, demonstrated that PFKFB2 is up-regulated as a consequence of the transcriptional changes by AR, with possible control through the AR-CAMKII-AMPK signaling pathway.

Other studies performing microarray analysis, using total RNA isolated from LNCaP cells treated with or without R1881 (methyltreinolone), a synthetic androgen, showed that androgens induce PFKFB2 expression in LNCaP cells (androgen-sensitive human prostate adenocarcinoma cells) by the direct recruitment of the ligand-activated AR to the PFKFB2 promoter. Moreover, depletion of PFKFB2 expression using siRNA (small interfering RNA) or inhibiting the PFK-2 activity with LY294002 (inhibitor of PI3K) treatment resulted in a reduced glucose uptake and lipogenesis, suggesting that the induction of de novo lipid synthesis by androgens requires the transcriptional up-regulation of PFKFB2 in prostate cancer cells (Moon et al., 2011).

Gastric cancer

Note

PFKFB2 mRNA expression is increased in malignant gastric tumors as well as the expression of known HIF-1-dependent genes, Glut1 (glucose transporter 1) and VEGF (vascular endothelial growth factor), supporting the HIF-dependent character of the induction of expression of the PFKFB2 (Bobarykina et al., 2006).

Hepatocellular cancer

Note

In immuhistochemistry samples of hepatocellular carcinoma, it has been recently found that high expression of MACC1 (metastasis associated in colon cancer 1), a key regulator of the HGF/Met-pathway, correlates with high expression of PFKFB2. This correlation has an effect on TNM stage (classification of malignant tumors), overall survival and Edmondson-Steier classification (Ji et al., 2014).

Papillary thyroid cancer

Note

The extent and presentation of papillary thyroid cancer (PTC) in adolescents and young adults (AYAs) is different than in older patients. This difference may be due to several candidate genes that are differentially expressed and which may have important roles in tumor cell biology. One of these genes is PFKFB2 but future functional genomics studies are needed to shed further light on whether a biologic basis exists to account for the disparity in AYA cancer incidence and outcome (Vriens et al., 2011).

Heart diseases

Note

In the heart, acute ischemia induces rapid activation of AMPK which phosphorylates Ser 466 leading to a two-fold increase in the V_{max} of PFKFB2 (Hue et al., 2002). mRNA analysis indicated that PFKFB2 is expressed at high levels not only in the heart but also in the brain and lungs. However, in vivo experiments showed that hypoxia induce moderate expression in the lung and liver and very strong stimulation in the testis. No induction or even mild inhibition was found in the heart, kidney, brain and skeletal muscle. Myocardial ischemia induces a shift to anaerobic metabolism, with a rapid stimulation of glycolysis (Wang et al., 2008).

Tetralogy of Fallot (TOF) is a heart defect in children that results in chronic progressive right ventricular pressure overload and shunt hypoxemia. Western blot, RT-qPCR (real time PCR) and immunohystochemical analysis revealed that PKFB2 expression and mRNA of PFKFB2 increased significantly in TOF patients.

Like tumors, under pathological stress conditions, cardiomyocytes gradually come to rely on glycolysis to satisfy their main energy requirements.

That is why these results suggest that PFKFB2 plays an important role in certain biological processes related to cardiac remodeling, which occurs in response to chronic hypoxia and long-

term pressure overload in TOF patients (Xia et al., 2013).

Glycolysis increases in cognitive heart failure (CHF), cardiac hypertrophy and cardiac ischemia (Neely et al., 1975).

Some studies producing mice with chronic and stable elevation of cardiac Fru-2,6-P_2 showed significant change in cardiac metabolite concentrations, increased glycolysis, reduced palmitate oxidation and protection of isolated myocytes from hypoxia.

Taken together, these results show that PFKFB2 is one of the enzymes that control cardiac glycolysis, producing an increase in Fru-2,6-P_2, causing detrimental effects and suggesting that the elevation of glycolysis in failing hearts could be injurious to an already compromised heart (Wang et al., 2008).

Inflammation

Note

It has been shown that purified human CD3+ T cells express PFKFB2 (Telang et al., 2012).

CCL5 (proinflammatory chemokine) treatment of ex vivo activated human CD3+ T cells induced the activation of the nutrient-sensing kinase AMPK and downstream substrates like PFKFB2, suggesting that both glycolysis and AMPK signaling are required for efficient T cell migration in response to CCL5, relating therefore PFKFB2 with T-cell activation and migration (Chan et al., 2012).

Mental disorders

Note

Schizophrenia presents impaired glucose regulation. Stone et al. (2004), using a genome scan, found that PFKFB2 shows linkage with schizophrenia in a multiple sample of subjects (European-American samples).

However, it is necessary to replicate these results with other samples and if PFKFB2 contributes on the liability for schizophrenia, its influence is likely to be modest, as most cases of schizophrenia are likely to result from multiple factors.

Growth restriction and development

Note

Infants with intrauterine growth restriction (IUGR) have a low weight at birth as a result of pathologic restriction of fetal growth (Wollmann, 1998). cDNA microarrays, RT-qPCR and Western blot analysis revealed that PFKFB2 expression increases in placentas from pregnancies with IUGR causing hypoglycemia.

However, further studies have to be performed in order to elucidate the role of PFKFB2 in glucose metabolism on IUGR placenta (Lee et al., 2010).

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