VCP (valosin containing protein)

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Identity

Other names: ALS14, IBMPFD, TERA, p97
HGNC (Hugo): VCP
Location: 9p13.3

DNA/RNA

Description
The p97/VCP gene spans a genomic region of 16674 bases on minus strand. The DNA of p97/VCP consists of 17 exons and the coding sequence starts in the first exon.

Transcription
The p97/VCP gene has one protein coding transcript which is 3859 bp long (Accession Number: NM_007126.3). The DNA has been cloned and sequenced by Koller and Brownstein in 1987 (Koller and Brownstein, 1987).

Pseudogene
According to Hoyle et al., p97/VCP has a mouse pseudogene namely Vcp-rs (valosin containing protein, related sequence) (Hoyle et al., 1997). For further information: Ensembl, Vega.

Protein

Description
VCP (Ter94 in D. melanogaster and CDC48 in S. cerevisiae) is a member of the AAA (ATPase associated with various cellular activities) ATPase family. It is one of the most abundant cytosolic proteins conserved throughout evolution from archaea to mammals.

The complete protein contains 806 amino acids. The calculated molecular weight of p97/VCP is 89322 Da and the basal isoelectric point is 5.14.

p97/VCP functions as a homohexamer composed of six subunits. Each protomer composed of four domains vital for its proper functioning, namely the N domain (1-187), D1 weak ATPase (209-460), D2 the major ATPase (481-761), and C (762-806) domains (DeLaBarre et al., 2006; Pye et al., 2007). p97/VCP gene consists of 17 coding exons.

Its N domain is encoded by exons 1, 2, 3, 4 and 5, while the D1 and D2 domains are encoded by exons 6, 7, 8, 9, 10 and 12, 13, 14, respectively.

There are two linker domains in the protein: N-D1 linker and flexible D1-D2 linker.

Genomic location of VCP/p97 gene at chromosome 9p13.3 (minus strand).
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The N domain of p97/VCP is responsible for the cofactor and ubiquitin binding function (Wang et al., 2003; Ye et al., 2003). While the D1 domain mediates oligomerization independent nucleotide binding, the D2 domain confers most of the ATPase activity (Wang et al., 2003). The two AAA domains contain the conserved Walker A, Walker B and a second region of homology (SRH). Walker A is required for nucleotide binding, whereas Walker B and SRH motifs mediate efficient ATP hydrolysis. ATP binding and hydrolysis lead to changes in the conformation of the hexameric ring, which is consistent with its role as a chaperone in disassembling protein complexes and mediating extraction of ubiquitinated proteins from the ER (Bays and Hampton, 2002; Rouiller et al., 2002).

Expression
Northern blot analyses showed that p97/VCP was ubiquitously expressed in all tissues and throughout the brain (Hirabayashi et al., 2001).

Localisation
Cytosol, nucleus. p97/VCP is recruited to the cytoplasmic surface of the ER via interaction with Endoplasmic reticulum-ubiquitin ligases.

Function
p97/VCP functions as segregase or unfoldase by utilizing the energy derived from ATP hydrolysis for conformational changes of target proteins. It is an essential protein having many roles in diverse biological processes, such as endoplasmic reticulum-associated degradation (ERAD), homotypic membrane fusion, transcriptional control, cell cycle regulation, autophagy, endosomal sorting and regulating protein degradation at the outer mitochondrial membrane (Woodman, 2003; Wang et al., 2004; Meyer et al., 2012). The diversity in cellular functions of p97/VCP is dictated by the variety of its interacting partner proteins. For example, p97/VCP has function in membrane fusion function via two different cofactors p47 and p37 (Uchiyama et al., 2006). The UBX-containing protein p47 functions together with p97/VCP in the fragmentation process of Golgi stacks during mitosis and for their reassembly after mitosis (Uchiyama et al., 2002; Uchiyama et al., 2003). The p97/VCP-p37 complex also brings about Golgi membrane fusion, however it might be required for organelle maintenance during interphase as well as their reassembly during mitosis (Uchiyama et al., 2006). p97/VCP has critical roles not only in Golgi...
membrane fusion but also in ER membrane fusion and nuclear assembly (Latterich et al., 1995; Hetzer et al., 2001).

p97/VCP forms another complex with Ufd1-Npl4 dimer (Ye et al., 2001; Braun et al., 2002; Jarosch et al., 2002; Rabinovich et al., 2002). This complex is involved in regulating spindle disassembly at the end of mitosis, assembly of the nuclear envelope and retro-translocation during ERAD by binding ubiquitinated proteins and exporting them from the ER to the cytoplasm (Hetzer et al., 2001; Cao et al., 2003). Another molecular machinery where p97/VCP interacts with ubiquitin ligases, gp78 and Hrd1 functions in ERAD (Zhong et al., 2004; Lilley and Ploegh, 2005). Through this interaction p97/VCP is recruited from the cytosol to the ER. The role of p97/VCP in ERAD is to interact with polyubiquitinated proteins and retrotranslocate them from ER to the cytosol. It has been recently suggested that Hrd1-mediated ERAD requires well-established retrotranslocation machinery, the p97/VCP-Ufd1-Npl4 complex, whereas the gp78 pathway needs only p97/VCP and Npl4 (Ballar et al., 2011). Another role of p97/VCP in ERAD is to bridge the ER to the proteasome by forming a complex with mHR23B (homolog of yeast Rad23)-PNGase (Li et al., 2005).

p97/VCP is also indicated in autophagy where it is required for the autophagosome and lysosome fusion and this function is impaired with mutations in IBM/PFD disease (Ju and Weihl, 2010; Tresse et al., 2010).

Additionally, p97/VCP has role in endolysosomal sorting, where it binds to monoubiquitinated cargo, caveolin, on endosomes and functions in Cave1 transport to the endolysosomes (Ritz et al., 2011). There are several reports linking p97/VCP to the DNA repair mechanism (Ramadan, 2012). Ubiquitin binding domain containing DVC1 protein recruits p97/VCP to DNA damage sites, where p97/VCP facilitates the extraction of the translesion synthesis (TLS) polymerase (Pol) η during DNA repair (Davis et al., 2012). p97/VCP also promotes recruitment of human tumor suppressor 53BP1 by removing Polycomb protein L3MBTL1 from chromatin (Acs et al., 2011).

p97/VCP has an essential role in DNA replication and cell cycle progression (Deichsel et al., 2009; Mouy et al., 2012). Moreover, p97/VCP has a central regulatory role in the coordination of licensing and elongation events during eukaryotic DNA replication (Franz et al., 2011). A recently identified role of p97/VCP is related to mitophagy (Tanaka et al., 2010). The Vms-Npl4-Cdc48 complex organized upon mitochondrial stress plays a role in maintaining the mitochondrial function via protein quality control (Heo et al., 2010). p97/VCP also functions in degradation of mitochondrial proteins and retrotranslocates these proteins from mitochondria to the cytosol for proteasomal degradation (Xu et al., 2011).

**Homology**

Human p97/VCP gene is homolog to murine and rattus p97/VCP with 99.3%.  

**Mutations**

**Somatic**  

There are several p97/VCP mutations identified related with Inclusion body myopathy associated with Paget disease of the bone and frontotemporal dementia (IBM/PFD) and amyotrophic lateral sclerosis (ALS).

**Implicated in**

**Inclusion body myopathy associated with Paget disease of the bone and frontotemporal dementia (IBM/PFD)**

**Note**

This rare proteinopathy, affecting mainly muscle, brain and bone, is associated with mutations in the p97/VCP gene (Watts et al., 2004). Muscle biopsies in IBM/PFD patients have revealed the presence of rimmed vacuoles, cytoplasmic inclusion bodies and p97/VCP aggregates in scattered muscle fibers (Watts et al., 2004). IBM/PFD neuropathologic changes are characterized by ubiquitin-positive neuronal intranuclear inclusions and dystrophic neurites mainly abundant in the neocortex (Forman et al., 2006).

There are 26 mutations in p97/VCP identified so far in IBM/PFD patients and these mutations are primarily in the N-terminal domain involved in ubiquitin binding and protein-protein interactions (Nalbandian et al., 2012).

**Amyotrophic lateral sclerosis (ALS)**

**Note**

Mutations in p97/VCP gene have been recently found also in familial cases of amyotrophic lateral sclerosis (ALS). A study using whole exome sequencing identified a pathogenic p97/VCP variant in an autosomal dominant Italian family with an ALS phenotype, and subsequently found that p97/VCP mutations were present in ~1-2% of our large cohort of familial ALS cases from unrelated families (Johnson et al., 2010). Whereas, no mutations were identified indicating that p97/VCP mutations do not have main contribution of classic ALS among Australian cases and Italian population (Tiloca et al., 2012; Williams et al., 2012). The p97/VCP expression was found to be increased in the skin of ALS patients (Ishikawa et al., 2012).

**Hepatocellular carcinoma**

**Note**

miRNA-129-5p downregulates p97/VCP expression and this regulation plays an important role in the progression of hepatocellular carcinoma (Liu et al., 2012).
2012). p97/VCP expression was found to be prognostic significant for disease-free and overall survival of patients with hepatocellular carcinoma (Yamamoto et al., 2003).

**Colorectal carcinoma**

*Note*

There is one study with 129 patients showing an association between high level-expression of p97/VCP with colorectal cancer prognosis (Yamamoto et al., 2004d).

**Esophageal carcinoma**

*Note*

The prognostic significance of p97/VCP expression in 156 esophageal squamous cell carcinoma (ESCC) patients has been revealed by Yamamoto et al. in 2004 (Yamamoto et al., 2004b).

**Prostate cancer**

*Note*

Elevated expression of p97/VCP has been associated with poor prognosis of prostate cancer with the study performed by analyzing p97/VCP expression in 136 patients (Tsujimoto et al., 2004).

**Breast cancer**

*Note*

The p97/VCP gene is underexpressed in patients who died of breast cancer within 5 years of surgery compared to patients who survived disease-free for more than 5 years (Asaka et al., 2006). Increased serum p97/VCP levels were observed in clinically significant proportions of breast cancer patients (Lagüé et al., 2012).

**Pancreatic cancer**

*Note*

A global genomic analysis of pancreatic cancer has confirmed p97/VCP overexpression and association with tumor metastasis by Serial Analysis of Gene Expression (SAGE). Other studies have indicated the generalized role of UPS in regulating the metastatic potential of pancreatic cancer (Jones et al., 2008). Increased expression of p97/VCP is associated with lymph node metastasis and prognosis of pancreatic ductal adenocarcinoma (Yamamoto et al., 2004a).

Moreover, elevated serum p97/VCP levels were detected in clinically significant proportions of patients with pancreatic cancer (8 of 12) (Lagüé et al., 2012). p97/VCP was also found to be a useful marker in detecting malignant behavior of pancreatic endocrine neoplasms (Yamamoto et al., 2004d).

**Gingival squamous cell carcinoma**

*Note*

It has been shown that the expression level of p97/VCP may be used as prognostic marker for gingival squamous cell carcinoma (GSCC) (Yamamoto et al., 2004c).

Moreover, the expression patterns of PBX2, a strong prognostic factor in GSCC, and p97/VCP proteins were evaluated in 66 subjects with GSCC who underwent curative surgery, and high PBX2 expression was associated with high p97/VCP expression (Qiu et al., 2012).

**Thyroid carcinoma**

*Note*

A study examining the p97/VCP expression in 332 patients who underwent operation for differentiated thyroid carcinoma showed that increased expression of valosin-containing protein (p97) is correlated with disease recurrence in follicular thyroid cancer (Yamamoto et al., 2005).

**Non-small cell lung carcinoma**

*Note*

Elevated p97/VCP expression is correlated with the progression and clinical prognosis of non-small cell lung carcinoma (NSCLC) (Yamamoto et al., 2004c).

Moreover, p97/VCP inhibition suppressed proliferation, induced G0/G1-phase cell cycle arrest of NSCLCs and migration in H1299 cells and reduced NSCLC tumor growth in both in vitro and xenograft murine (athymic-nude) models after EerI treatment (Valle CW et al., 2011).

**Gastric cancer**

*Note*

Expression level of p97/VCP was found to be associated with prognosis and progression of gastric cancer (Yamamoto et al., 2003).

**Leukemia**

*Note*

Monocytic differentiation and G0/G1 growth arrest in human U937 leukemia cells is accompanied by an increase in VCP/p97 expression and a distinct subcellular distribution to be reverted during retrodifferentiation (Bertram et al., 2008). Furthermore, high p97/VCP expression has been shown to be associated with poor prednisone response in childhood acute lymphoblastic leukaemia patients (Lauten et al., 2006).

**Osteosarcoma**

*Note*

A study on osteosarcoma indicates the function of p97/VCP as a regulator of NFkB mediated tumor metastasis (Asai et al., 2002).

**Neurodegeneration**

*Note*

Excessive accumulation of misfolded proteins may inactivate p97/VCP in several neurodegenerative disorders, eventually leading to the neurodegenerations (Hirabayashi et al., 2001; Hsueh, 2012).
**Werner syndrome**

**Note**

It has been proposed that a novel role for p97/VCP in the DNA damage response pathway via modulating the availability of Werner protein, mutations of which causes Werner syndrome, a genetic disorder characterized by premature onset of aging symptoms (Partridge et al., 2003; Indig et al., 2004).

**Machado-Joseph disease**

**Note**

Expansion of a polyglutamine tract in ataxin-3 (AT3), a deubiquitylating enzyme, results in spinocerebellar ataxia type 3/Machado-Joseph disease. AT3 interacts with p97/VCP and regulates flow through the ERAD pathway by modulating VCP-dependent extraction of proteins from the ER (Zhong and Pittman, 2006). Furthermore, p97/VCP was shown to be an activator specifically of wild-type ataxin-3, exhibiting no effect on expanded ataxin-3 (Laco et al., 2012).

**Hepatitis**

**Note**

Hepatitis B virus X protein (HBx protein) transactivates NF-κB, which is important in the pathogenesis of HBV-related diseases. It has been shown that HBx interacts with VCP, and enhances the VCP-mediated activation of NF-κB (Jiao et al., 2011).

**Chronic obstructive pulmonary disease and emphysema**

**Note**

There is a study correlating the higher expression of valosin-containing protein (VCP) retrograde translocation complex (VCP-Rma1-gp78) with severity of emphysema in chronic obstructive pulmonary disease (COPD) lung tissues and over-expression of inflammatory, ER stress and apoptotic mediators like NFκB, GADD-153/CHOP, and p-eIF2α (Min et al., 2011).

**Cholesterol**

**Note**

Insig-1, a negative regulator of cholesterol synthesis is rapidly degraded by proteasomes when cells lack of cholesterol, and its degradation is inhibited when sterols accumulate. p97/VCP was shown to recruit proteasomes to Insig-1 before extraction from membrane (Ikeda et al., 2009). It is also known that ubiquitinated 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) is recognized by the ATPase VCP/p97, which mediates extraction and delivery of reductase from ER membranes to cytosolic 26 S proteasomes for degradation (Hartman et al., 2010).

**Antiviral immunity**

**Note**

p97/VCP is implicated as a host factor in antiviral immunity, where depletion or catalytic inhibition of p97/VCP prevents capsid degradation and reduces neutralization (Hauler et al., 2012).

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