Abstract

PARK7 (also called DJ-1 or Parkinsonism associated deglycase) is a pleiotropic protein belonging to the peptidase C56 family. It acts as a positive regulator of androgen receptor-dependent transcription, redox-sensitive chaperone, sensor for oxidative stress, and apparently protects neurons against oxidative stress and cell death. Dysfunctions in PARK7 are related to autosomal recessive early-onset Parkinson disease 7 and cancer forms. Here, we review some major data on PARK7, concerning the genetic structure, the transcription regulation, the encoded protein and functions, and its implication in human diseases.

Keywords: PARK7, DJ-1, Autosomal Recessive Early-Onset Parkinson Disease, Oncogene

Identity

Other names: DJ1, DJ-1, HEL-S-67p, RS, CAP1, FLJ27376, FLJ92274, FLJ34360

HGNC (Hugo): PARK7

Location: Location Cytogenetic location: 1p36.23; Molecular location: Chromosome 1; Start 7961654; Stop 7985282 based on Genome Browser Human Dec. 2013 (GRCh38/hg38) Assembly [Link to chromosome band 1p36]

Local order: PARK7 is flanked towards the telomeric direction by two protein-coding genes (UTS2 and TNFRSF9) and towards the centromeric direction by ERRFI1. According to NCBI MapViewer, a non-coding RNA (LOC105376694) is also present in this locus (Figure 1).
DNA/RNA

**Description**

DJ-1 maps on the distal part of the short arm of chromosome 1, cytoband 1p36.23 (Figure 1). It spans about 24 kb and includes eight exons (Figure 2). The first two exons (1A and 1B) are noncoding and alternatively spliced in the DJ-1 mRNAs (Bonifati, Rizzu, Squitieri, et al., 2003).

**Transcription**

Currently, the NCBI RefSeq database annotates two representative transcripts as full-length PARK7 mRNAs (Figure 2). However, a total of 10 spliced variants is reported in the Ensembl database http://www.ensembl.org (Figure 3). The majority of mRNAs contain a 570 bp ORF, encoding a protein of 189 aa. Two shorter transcripts (PARK7-003 lacking exon 4, and PARK7-010 starting at an inner transcription point) produce smaller proteins (169 and 160 aa respectively) (Table 2 and Fig. 3). Other transcripts do not encode proteins and are processed via the NMD (non-sense mediated decay) mechanism.

**Pseudogene**

PGOHUM00000239770: Chr. 12, Start Coordinate 49988931, Stop Coordinate 49989471 according to Genome Browser Human Dec. 2013 (GRCh38/hg38) Assembly

PGOHUM00000236716: Chr. 9, Start Coordinate 98680419, Stop Coordinate 98680983 according to Genome Browser Human Dec. 2013 (GRCh38/hg38) Assembly

**Protein**

**Description**

X-ray crystallographic examination of DJ-1 protein structure indicates that it exists as a dimer (Figure 4)(Wilson et al., 2003). It contains domains found in heat shock chaperones and belongs to the ThiJ/PfpI family. This family (pfam01965) includes: ThiJ, a protein involved in thiamine biosynthesis in prokaryotes; PfpI (so-called from P. furious protease I) and other bacterial proteases; araC and other bacterial transcription factors; and the glutamine amidotransferases family (including bacteria catalases) (Bonifati, Rizzu, Squitieri, et al., 2003).

**Expression**

DJ-1 is a ubiquitous protein, highly expressed in almost all cells and tissue (Figure 5). Distribution studies indicate that DJ-1 is preferentially expressed in testis, brain and kidney. In the brain, DJ-1 is expressed in both neurons and glial cells. The expression level of DJ-1 is increased under oxidative stress conditions both in PD and other neurodegenerative diseases (Ariga et al., 2013). DJ-1 is also frequently overexpressed in the several tumor types (Cao et al., 2015).

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Table 1.
Localisation

Subcellular localization: DJ-1 is mainly localized in the nucleus, cytoplasm, and mitochondria and is secreted into culture medium or serum, cerebrospinal fluid, saliva and nipple fluid (Ariga, 2015). DJ-1 is translocated from the cytoplasm to nucleus upon addition of a mitogen to the culture medium, while it translocates to mitochondria after oxidative stress (Junn et al., 2009).

Function

The product of DJ-1 is an 189 amino acidic highly conserved multifunctional protein belonging to the peptidase C56 family (Lev et al., 2006). It mainly acts as regulator of transcription, redox-sensitive chaperone, sensor for oxidative stress, cysteine protease, and seems to protect neurons from ROS-induced apoptosis (Figure 7) (Xu et al., 2005; Ariga et al., 2013).

The oxidative stress sensor activity is carried out by three cysteine residues at C46, C53 and C106; under oxidative stress conditions, C106 is firstly oxidized from SH to SOH, SO2H and to SO3H form. The other cysteine residues then follow the same process of oxidation.

The regulation of transcription is mediated by DJ-1 binding with various transcription factors without directly tie up to DNA. Transcription factors or modified proteins identified so far include TP53, the androgen receptor AR and its regulatory proteins, the polypyrimidine tract-binding protein-associated splicing factor (SFPQ), KEAP1, an inhibitor for nuclear factor erythroid-2 related factor 2 (NFE2L2), the sterol regulatory element-binding protein (SREBP), Ras-responsive element-binding protein (RREB1), and signal transducer and activator of transcription 1 (STAT1) (Ariga, 2015).

DJ-1 is also involved in the activation or repression of cell growth and cell death signaling pathways. Specifically, this polypeptide modulates p53 activity, the PI3K/Akt pathway by interacting with PTEN, and intervenes in the Raf/Erk pathway together with ras (Ariga, 2015). To this regard, it should be reminded that the first identified DJ-1 function was its oncogene activity transforming mouse NIH3T3 cells in cooperation with activated ras (Nagakubo et al., 1997).
Figure 5 (adapted from PROTEOMICS DB - www.proteomicsdb.org) shows the central and peripheral distribution of DJ-1 in human tissues. It is a ubiquitous protein, expressed in almost all human body systems.

Figure 6 (from GeneCards database http://www.genecards.org/ and based on Compartments http://compartments.jensenlab.org/) shows the subcellular localizations of DJ-1 into cellular structures. Data are derived from database annotations, automatic text mining of the biomedical literature, and sequence-based predictions. The confidence of each association is indicated with numbers (the higher number corresponds to a greater confidence).
Figure 7 summarizes the functions of DJ-1 and related diseases. It is thought that excess of activation or loss of function of DJ-1 triggers the onset of various diseases, including cancer and oxidative stress-related diseases. Abbreviations: PD - Parkinson's Disease, FAP - familial amyloid polyneuropathy; COPD - chronic obstructive pulmonary disease. Adapted from (Ariga, 2015).

Homology
The PARK7 Gene Tree shows a great evolutionary conservation across species (Figure 8). The internal nodes of the phylogenetic tree are annotated for duplication (red boxes) and speciation (blue boxes) events, which correspond to paralogs and orthologs genes respectively.

Mutations
Somatic
See Table 2.

Germinal
A wide spectrum of mutations in PARK7 have been identified in familial Parkinson's Disease patients from different ethnicities. Mutations include missense mutations in coding and UTR regions, frame-shifts, copy number variations, and splice sites alterations (Table 2).

Somatic
Along with the germinal mutations occurring in Parkinson's Disease, genetic defects have also been observed in solid tumors. A list of the known cancer-derived mutations is available at the COSMIC Database and is summarized in Figure 9.

Epigenetics
No currently known epigenetic mechanisms regulating PARK7.

Implicated in

Parkinson's Disease
Mutations in PARK7 are the less common cause of autosomal recessive Parkinsonism (~ 1% of early-onset PD) (Lockhart et al., 2004; Moore et al., 2005). The first identified mutations were a large homozygous deletion and a missense mutation (L166P) identified in both Italian and Dutch consanguineous families (van Duijn et al., 2001; Bonifati, Rizzu, Squitieri, et al., 2003). The other observed familial mutations are summarized in Table 2.

Familial amyloid polyneuropathy
Transthyretin (TTR), a protein causing familial amyloidotic polyneuropathy (FAP), is a substrate of DJ-1 protease (Koide-Yoshida et al., 2007). In normal conditions, both TTR and DJ-1 are secreted into the culture medium. Under oxidative stress, TTR but not DJ-1 is secreted into the culture medium, resulting in the aggregation of TTR protein. Mirror images of both the expression patterns and solubility of DJ-1 and TTR have been observed in tissues of FAP patients, and the unoxidized form of DJ-1 is secreted into the serum of FAP patients. These results suggest that oxidative stress abrogates secretion of DJ-1 and that secreted DJ-1 degrades aggregated TTR to protect against the onset of FAP (Koide-Yoshida et al., 2007).

Chronic obstructive pulmonary disease
Disease
Chronic obstructive pulmonary disease (COPD) is caused by cigarette smoking and oxidative stress. Malhotra et al. assessed the expression of NFE2L2 (NRF2) and DJ-1 in non-COPD and smoker COPD lungs and in cigarette smoke-exposed human lung epithelial cells (Beas2B) and mice (Malhotra et al., 2008). COPD patient lungs showed significantly decreased DJ-1 levels. Exposure of Beas2B cells to cigarette smoke caused oxidative modification and enhanced proteasomal degradation of DJ-1 protein. Disruption of DJ-1 in mouse lungs, mouse embryonic fibroblasts, and Beas2B cells lowered NRF2 protein stability and impaired antioxidant induction in response to cigarette smoke. Overall, DJ-1 expression was negatively associated with severity of COPD (Malhotra et al., 2008).
<table>
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<th>PARK7 Mutations</th>
<th>Exon</th>
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<tr>
<td>Ex1-5del (g.07561_21658del14098)</td>
<td>EX1-5</td>
<td>(Bonifati, Rizzu, van Baren, et al., 2003)</td>
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<td>Ex1-5dup (breakpoints not mapped)</td>
<td>EX1-5</td>
<td>(Macedo et al., 2009)</td>
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<td>Ex2del (breakpoints not mapped)</td>
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</table>

Table 2 displays the currently known PARK7 genetic mutations related to familial Parkinson's Disease. Details are available at the Parkinson Disease Mutation Database (http://www.molgen.vib-ua.be/PDMutDB/).
Figure 8. The PARK7 Gene Tree shows the maximum likelihood phylogenetic tree representing the evolutionary history of this gene, constructed using the alignment of a representative protein for each species (green bars). This Gene tree has been generated by Ensembl (GeneTree ENSGT00000001231).
Figure 9 shows the overall distribution of PARK7 somatic mutations in cancer listed in COSMIC Database (http://cancer.sanger.ac.uk/cosmic) (March 2016). The exact number of collected somatic mutations in different cancer types is indicated in the data labels.

**Type II Diabetes**

The expression of DJ-1 is reduced in pancreatic islets of patients with type 2 diabetes mellitus (T2DM). Under non-diabetic conditions, DJ-1 expression increases in mouse and human islets during aging. Jain et al. demonstrated that, in mouse islets, DJ-1 prevents an increase in reactive oxygen species and preserves mitochondrial integrity and physiology, prerequisites for glucose-stimulated insulin secretion (Jain et al., 2012). Accordingly, DJ-1 deficient mice developed glucose intolerance and reduced β-cell area as they age or gain weight. These data suggested that DJ-1 is more generally involved in age- and lifestyle-related human diseases and show that DJ-1 plays a key role in glucose homeostasis (Jain et al., 2012).

**Stroke**

Loss of DJ-1 increases the sensitivity to excitotoxicity and ischemia, whereas expression of DJ-1 can reverse this sensitivity and provide protection (Aleyasin et al., 2007). Importantly, DJ-1 expression decreases markers of oxidative stress after stroke insult in vivo, suggesting that DJ-1 protects through alleviation of oxidative stress (Aleyasin et al., 2007). Consistent with this finding, Aleyasin et al., 2007 demonstrated the essential role of the oxidation-sensitive cysteine-106 residue in the neuroprotective activity of DJ-1 after stroke.

**Prostate cancer**

The intracellular level of the DJ-1 polypeptide in prostatic benign hyperplasia (BPH) cells is inducible and results markedly increased after exposure to stress-inducing agents (H₂O₂ and mitomycin C). The expression of DJ-1 is relatively high in PC-3 cells at the constitutive level, and incubation with the same cytotoxic drugs does not further modulate the polypeptide expression. Both cytotoxic agents activate the apoptotic pathway in the benign prostatic cells but not in PC-3 cells, which are resistant to their action (Hod, 2004).

**Renal carcinoma**

The expression level of DJ-1 mRNA in a series of 176 renal cell carcinomas (RCC) has been measured by (Sitaram et al., 2009). The level of DJ-1 has been demonstrated significantly elevated in clear cell RCC compared with papillary RCC and kidney cortex tissue.

**Hepatocellular carcinoma**

DJ-1 was found significantly up-regulated in 149 hepatocellular carcinomas (HCC). DJ-1 expression correlates with preoperative alpha-fetoprotein, liver cirrhosis, vein invasion, differentiation and overall survival, thus suggesting DJ-1 as a candidate prognostic biomarker of HCC (S. Liu et al., 2010).

**Ovarian carcinoma**

The expression and clinical role of DJ-1 and its putative association with transcriptional regulators specific proteins (SP1 and SP3) were investigated in ovarian carcinoma by (Davidson et al., 2008). RT-PCR reactions and immunohistochemistry were used to analyze the expression levels of DJ-1, Sp1 and Sp3 mRNAs and PTEN protein. DJ-1 expression resulted positively associated with Sp1 expression in effusions, and with Sp1 and Sp3 expression in solid tumors. Overall, results show DJ-1 is frequently expressed in advanced-stage ovarian carcinoma at all anatomical sites and is co-expressed with its transcriptional regulators Sp1 and Sp3. In contrast, PTEN expression is infrequent in this disease.

**Breast cancer**

Expression of DJ-1 was examined by immunohistochemistry and in-situ hybridization in 273 breast invasive ductal carcinomas (IDCs) and 41
breast ductal carcinomas in situ (DCISs) and in cancer cell lines (MDA-MB-231). DJ-1 protein expression resulted lower than adjacent non-cancerous epithelium in 6 of the 41 DCISs and in 146 of the 273 IDCs. Patients with IDC and low DJ-1 expression had significant shorter disease-free survival and overall survival. Low expression of DJ-1 protein seems to be predictive of poor outcome in patients with IDC (Tsuchiya et al., 2012). Furthermore, RS/DJ-1 was found to be secreted in the breast cell line SUM-44 and in sera of diagnosed patients with breast cancer (Le Naour et al., 2001).

Acute leukemia
DJ-1 was found overexpressed in acute leukemia (AL) patient samples and leukemia cell lines, giving the first clue that DJ-1 overexpression might be involved in leukemogenesis and/or disease progression of AL (H. Liu et al., 2008). Inactivation of DJ-1 by RNA-mediated interference (RNAi) in leukemia cell lines K562 and HL60 resulted in inhibition of the proliferation potential and enhancement of the sensitivity of leukemia cells to chemotherapeutic drug etoposide (H. Liu et al., 2008).

Cervical cancer
Normal cervical epithelium and patient-matched high-grade squamous intraepithelial lesions (HSIL) with cervical carcinoma tissue were compared by using laser capture microdissection and 2-D DIGE (Arnouk et al., 2009). Significant expression changes were observed with 53 spots corresponding to 23 unique proteins, including DJ-1. Results were confirmed by immunohistochemistry using either frozen sections from the same cohort or formalin fixed paraffin embedded samples from a tissue microarray. These markers can have potential applications for increasing the predictive value of current screening methods (Arnouk et al., 2009).

Non-small cell lung carcinoma
A proteomic approach using two-dimensional gels coupled with mass spectrometry was used in non-small cell lung carcinoma samples to identify proteins altered when treated with paclitaxel, a chemotherapeutic that activates mitogen

Pancreas adenocarcinoma
To identify potential novel biomarkers for pancreatic ductal adenocarcinoma (PDAC) from pancreatic juice, (Tian et al., 2008) carried out gel electrophoresis (DIGE) and tandem mass spectrometry (MS/MS) to compare the pancreatic juice profiling from 9 PDAC patients and 9 cancer-free controls. Of the differently expressed proteins, three up-regulated proteins in pancreatic cancer juice were selected for validation by Western blot and immunohistochemistry, including DJ-1. Up-regulation of DJ-1 was associated with better differentiation (Tian et al., 2008). In another study, the DJ-1 protein expression in tissue specimens from 41 patients was evaluated by immunohistochemistry and associated with a negative impact of chemotherapy with gemcitabine on patient's survival. Therefore, DJ-1 has been suggested as prognostic markers that express resistance of pancreatic cancer patients to chemotherapy with gemcitabine (Tsiaousidou et al., 2013).

Laryngeal squamous cell carcinoma
A study conducted by (Shen et al., 2011) aimed to explore the correlation between DJ-1 gene and survivin gene BIRC5 in laryngeal squamous cell carcinoma. The expression levels of DJ-1 gene and survivin gene in 82 laryngeal carcinoma tissues from patients and 82 negative surgical margin tissue samples were measured by immunohistochemistry and the relationship with clinicopathologic parameters was assessed. Positive correlations were
found between expression levels and patients’ clinical parameters in laryngeal carcinoma tissues and tumor stages, but not with lymph node metastasis. The DJ-1 gene expression level was also related to cell differentiation. DJ-1 and survivin play a vital role in the occurrence and development of laryngeal carcinoma. DJ-1 may promote the carcinogenesis of laryngeal cells by up-regulating the survivin gene expression (Shen et al., 2011).

**Esophageal squamous cell carcinoma**

The expression of DJ-1 in 81 esophageal squamous carcinoma (ESCC) tumors, 31 paired non-neoplastic esophageal epithelia, and 19 paired ESCC lymph node metastases was analyzed by (Yuen et al., 2008). They found that cytoplasmic DJ-1 expression was significantly higher in ESCC and ESCC lymph node metastases than in non-neoplastic esophageal epithelium. ESCC specimens with high distant metastatic potential also had a significantly higher level of nuclear DJ-1 expression. A high level of nuclear DJ-1 was significantly associated with poorer patient survival in the cohort (P = 0.028). DJ-1 expression was significantly associated with pAkt, whereas nuclear DJ-1 expression was significantly correlated with nuclear expression of DAXX. These results suggest that phosphatidylinositol 3-kinase pathway and Daxx-regulated apoptosis might be important in DJ-1-mediated ESCC progression. In conclusion, results suggest that DJ-1 plays a very important role in transformation and progression of ESCC and may be used as a prognostic marker in ESCC.

**Other malignancies**

Increased levels of DJ-1 expression have been observed in other kinds of cancer cells and tissues, including gastric cancer (Shimwell et al., 2012; Li et al., 2013), supraglottic cancer (Zhu et al., 2012), cholangiocarcinoma (Kawase et al., 2009), glioma/glioblastomas (Hinkle et al., 2011; Wang et al., 2013), bladder carcinoma (Lee et al., 2012) and melanoma (Pardo et al., 2006). Increased levels of DJ-1 expression in cancer cells are parallel to severity of cancer with poor prognosis, including metastasis and invasion (Ariga, 2015).

**To be noted**

COMPARTMENTS (compartments.jensenlab.org) is an updated web resource that integrates evidence on protein subcellular localization from manually curated literature, high-throughput screens, automatic text mining, and sequence-based prediction methods. It can be useful to display, with a certain grade of confidence, the subcellular localization of a specific biological molecule.

**PROTEOMICSDDB** (www.proteomicsdb.org) enables navigation of proteomes, provides biological insight and fosters the development of proteomic technology, and is a good tool to visualize the tissue distribution of mRNAs and proteins in human.

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