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Gene Section
Review

HTRA2 (HtrA serine peptidase 2)

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Identity

Other names: OMI, PARK13, PRSS25

HGNC (Hugo): HTRA2

Location: 2p13.1

Local order: Genes flanking HTRA2 in telomere to centromere direction:
- DQX1: DEAQ box RNA-dependent ATPase 1
- AUP1: ancient ubiquitous protein 1
- **HTRA2**
- LOXL3: lysyl oxidase-like 3
- DOK1: docking protein 1

Note

Amplification of 2p13-16 has frequently been found in non-Hodgkin's lymphoma, mediastinal thymic B-cell lymphoma and in some cases of neuroblastoma, ovarian cancer, squamous cell carcinoma of the head and neck, non-small cell lung cancer and synovial sarcoma (Knuutila et al., 1998). Translocations and deletions of region 2p12 were found in acute and chronic lymphocytic leukaemias as well as nonlymphocytic leukaemia and Hodgkin disease (Shapiro et al., 1994). Genetic variations on chromosome 2p12-p13 have been associated with the development of Parkinson's disease (Gasser et al., 1998), Miyoshi myopathy, limb-girdle muscular dystrophy (Liu et al., 1998), Welander myopathy (Ahlberg et al., 1999), acute lymphoblastic childhood leukaemia (Inaba et al., 1991), chronic lymphocytic leukaemia (Richardson et al., 1992) and Burkitt's lymphomas (Lenoir et al., 1982).

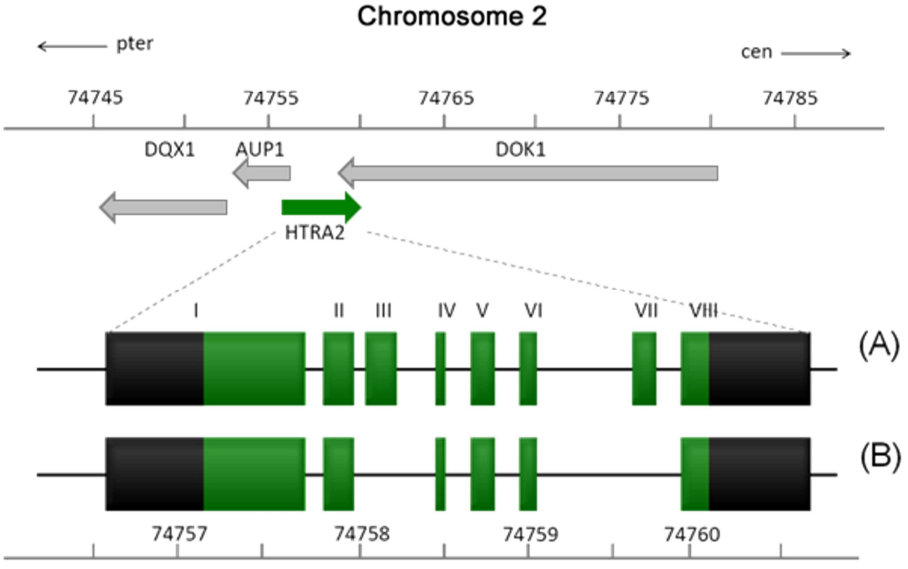

Figure 1. Localization and schematic organization of the HTRA2 gene on chromosome 2. The numbers indicate the length in kilo bases. Green boxes represent exons. Exons present in the full-length HTRA2 mRNA (A) and in the short form HTRA2 mRNA (B) are shown. Black boxes indicate untranslated regions.

DNA/RNA

Description

The HTRA2 gene encompasses 4152 bases of DNA. HTRA2 has a promoter region of about 300 bp which includes putative binding sites for Sp1, AP-2, Elk-1 and Nrf-2. The coding part is composed of eight exons (Figure 1). The 3' end of HTRA2 cDNA contains a 35 bp noncoding sequence (Faccio et al., 2000b).

Transcription

Two alternatively spliced variants of HTRA2 mRNA have been sequenced, a full-length variant, length of 2550 bases, and a short form mRNA, length of 2259 bases (Figure 1). Additional transcript variants have also been described but their sequences have not been determined.

The full-length HTRA2 mRNA has an open frame of 1377 bases and is expressed ubiquitously. The gene encodes a 50 kDa protein of 458 amino acids residues (Faccio et al., 2000a). The short form HTRA2 mRNA, lacking two exons: III and VII, is expressed predominantly in the kidney, colon and thyroid (Faccio et al., 2000b).

A single-nucleotide polymorphism (SNP) rs1183739 located in the HTRA2 5'UTR has been found in patients with Parkinson's disease (PD). The sequence change is located 586 base pairs upstream of the transcriptional start site of the HTRA2 gene (-586G>C). In vitro transcriptional study revealed that the SNP is associated with an increased expression of the HTRA2 gene in SH-SY5Y and HEK293 cells (Bogaerts et al., 2008a). Other SNPs, the -442C>T mutation identified in the HTRA2 5'UTR and the g.53572436C>G mutation identified in the regulatory region of the gene were found to decrease the HTRA2 expression (Bogaerts et al., 2008a).

The HTRA2 gene expression increases in response to cellular stresses causing aberrations in protein structure such as the heat or oxidative shocks, tunicamycin or cisplatin treatment (Gray et al., 2000; Faccio et al., 2000a; Cilenti et al., 2005; Han et al., 2008; Zurawa-Janicka et al., 2008). Upon accumulation of misfolded proteins in the mitochondrial intermembrane space an enhanced expression of HTRA2 as a consequence of ligand-independent activation of estrogen receptor alpha activity has been demonstrated (Papa and Germain, 2011). It was also shown that transcription of the HTRA2 gene is controlled by p53 protein. Enhanced expression of the gene has been observed in HeLa cells and primary mouse thymocytes treated with etoposide - an agent inducing apoptotic cell death triggered by DNA damage (Jin et al., 2003).

Pseudogene

No pseudogenes have been identified.

Protein

Note

HtrA2 belongs to the HtrA family of evolutionarily conserved ATP-independent serine proteases, homologues of the HtrA (DegP) serine protease from the bacterium Escherichia coli. HtrA proteins are characterized by the presence of a trypsin-like protease domain with the catalytic triad His-Asp-Ser and at least one PDZ domain at the C-terminal end. General function of the HtrA proteins is the defence against cellular stresses (such as heat shock, oxidative stress) causing aberrations in protein structure. At least, four human HtrA proteins have been identified. They are involved in protein quality control, apoptosis and regulation of cell signaling. Disturbances in their functions contribute to neurodegenerative disorders and development of various types of cancer (reviewed by Chien et al., 2009; Clausen et al., 2011; Singh et al., 2011; Zurawa-Janicka et al., 2010).

Description

The HTRA2 gene encodes a polypeptide of 458 aa, mass of about 50 kDa. The full-length HtrA2 contains the N-terminal mitochondrial targeting sequence (1-40 aa), a transmembrane domain (105-125 aa), followed by a serine protease domain (150-343 aa) with the catalytic triad His198-Asp228-Ser306, and one PDZ domain (364-445 aa) at the C-terminal end (Figure 2). The transmembrane domain (TM) determines the topology of HtrA2 in the mitochondrial intermembrane space and anchors the proform of the protease in the inner membrane. The protease and the PDZ domains are exposed into the mitochondrial intermembrane space (Kadomatsu et al., 2007).

Upon activation HtrA2 undergoes proteolysis generating a 36 kDa mature form of the protease (134-458 aa) with the N-terminal AlaValProSer motif governing interaction with the Inhibitor of Apoptosis Proteins (IAPs).

Following apoptotic stresses the mature HtrA2 is released from the mitochondria into the cytosol (Suzuki et al., 2001; Hegde et al., 2002; Martins et al., 2002; Verhagen et al., 2002).

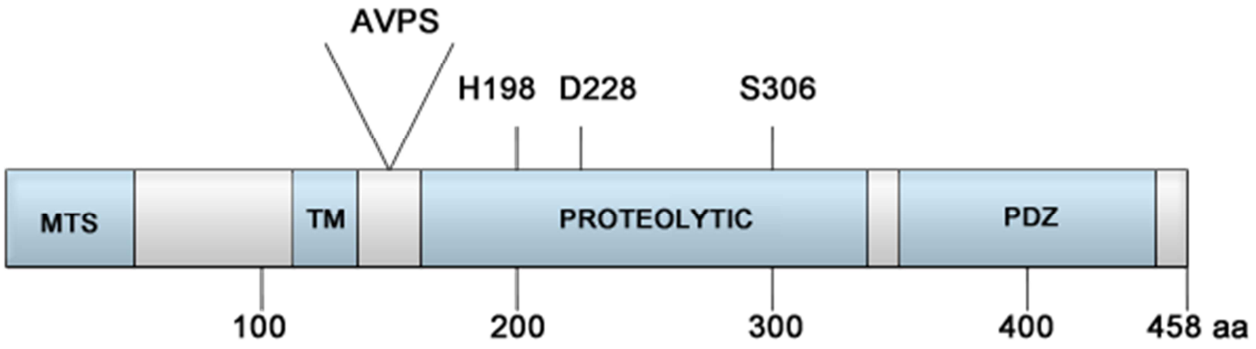

Figure 2. Domain organization of human HtrA2 protein. MTS: mitochondrial targeting signal, TM: transmembrane domain, PROTEOLYTIC: trypsin-like domain, PDZ: PDZ domain, AVPS: amino acids of the IAPs binding motif. Amino acid residues of the HtrA2 catalytic triad are marked (numbers indicate the position of the given residue in the polypeptide chain).

An X-ray crystallographic study showed that HtrA2 molecule is a pyramid-shaped homotrimer. The N-terminal IAPs binding motifs of monomers form the top of the trimer and the PDZ domains are located at the bottom of the structure (Li et al., 2002). Formation of the homotrimeric stucture has been confirmed by experimental data (Li et al., 2002; Nam et al., 2006). Oligomerization is mediated by the trimerization motif of the protease domain (146-151 aa) wherein phenylalanine at the residue 149 is suggested to be a major determinant of the trimeric assembly. It was also demonstrated that the formation of the homotrimer is required for the HtrA2 proteolytic activity (Li et al., 2002; Nam et al., 2006).

Expression

HTRA2 is expressed ubiquitously and quite uniformly among human tissues. However, the highest expression of HTRA2 was detected in fetal liver (Nie et al., 2003).

Localisation

HtrA2 is predominantly localized in the mitochondrium (Martins et al., 2002; Hegde et al., 2002; Verhagen et al., 2002). The proform of HtrA2 possessing the transmembrane region is anchored in the inner membrane with the proteolytic domain and the PDZ domain exposed into the intermembrane space (IMS). Mature form of HtrA2 without the TM region largely resides in the IMS as a soluble protein (Kadomatsu et al., 2007). The protein was also detected in the endoplasmic reticulum and nucleus (Faccio et al., 2000a; Gray et al., 2000; Marabese et al., 2008).

Function

HTRA2 functions as an ATP-independent serine protease.

It is believed that the primary function of HtrA2 is the maintenance of mitochondrial homeostasis. Under normal physiological conditions HtrA2 acts as a quality control factor and promotes cell survival. Disturbances of the HtrA2 proteolytic activity lead to the accumulation of unfolded proteins in mitochondria, dysfunction of the mitochondrial respiration, generation of reactive oxygen species, and result in a loss of mitochondrial competence (Jones et al., 2003; Martins et al., 2004; Krick et al., 2008; Moisoi et al., 2009). The Mnd2 (Motor neuron degeneration 2) mice carrying a loss-of-function missense HTRA2 Ser276 mutation as well as the knockout mice carrying a homologous deletion of the HTRA2 gene exhibit phenotypes with features typical for the Parkinsonian syndrome. Both, the mnd2 cells and the $HTRA2^{-/-}$ cells contain an increased number of atypical mitochondria and are more prone to death triggered by agents inducing intrinsic pathway of apoptosis (e.g. etoposide) and affecting mitochondrial functions (e.g. rotenone) (Jones et al., 2003; Martins et al., 2004).

In stressful conditions HtrA2 switches its function from protective to proapoptotic. HtrA2 induces apoptosis in a caspase-dependent manner as well as in a caspase-independent manner via its proteolytic activity. Upon apoptosis-inducing agents such as ultraviolet radiation (Martins et al., 2002; Trencia et al., 2004), staurosporine (Hegde et al., 2002; Munoz-Pinedo et al., 2006), cisplatin (Cilenti et al., 2004), etoposide (Jin et al., 2003), imatinib mesylate (Okada et al., 2004), botrezomib (Baou et al., 2010), H_2O_2 (Ding et al., 2009) HtrA2 undergoes proteolytic processing, resulting in the exposure of the N-terminal AlaValProSer motif which mediates interaction with the Inhibitor of Apoptosis Proteins (IAPs). Mature HtrA2 is then released from the mitochondria into the cytosol where it interacts with the IAPs such as XIAP (X-linked inhibitor of apoptosis protein), cIAP1 (cellular inhibitor of apoptosis protein-1), cIAP2, Apollon/BRUCE, through their BIR domains (Martins et al., 2002; Hegde et al., 2002; Verhagen et al., 2002; Yang et al., 2003; Srinivasula et al., 2003; Jin et al., 2003; Sekine et al., 2005). Degradation of the IAPs by HtrA2 leads to activation of caspases 3, 7 and 9, and facilitates cell death (Martins et al., 2002; Hegde et al., 2002; Verhagen et al., 2002; Seong et al., 2004). Kuninaka et al. (2005) showed that the serine-threonine

kinase WARTS serves as a regulator of the HtrA2 proteolytic activity towards IAPs. Depletion of WARTS diminishes degradation of XIAP and cIAP1, and prevents HtrA2-mediated apoptosis.
HtrA2 contributes to the induction of apoptosis by degradation of antiapoptotic proteins other than the IAPs, such as cytoplasmic ped/pea15 (Trencia et al., 2004) and mitochondrial HAX-1 (Cilenti et al., 2004), and also by proteolysis of p73 protein which enhances its proapoptotic activity. Upon induction of apoptosis HtrA2 is translocated to the nucleus where it cleaves p73. Proteolytically modified p73 stimulates transcription of the BAX gene, whose protein product exhibits proapoptotic function (Marabese et al., 2008).
The protease is an inductor of anoikis, cell death induced by cell detachment or loss of cell contact with the extracellular matrix. Resistance to anoikis is a common feature of cancer cells contributing to metastasis. Anoikis of non-maliganant intestinal epithelial cells triggered by cell detachment is mediated by down-regulation of Bcl-X_L followed by the release of mitochondrial HtrA2 into the cytosol. However, oncogenic Ras blocks the HtrA2 translocation and HtrA2-mediated cell death (Liu et al., 2006).
HtrA2 may also function as a chaperone protein. Results of the in vitro experiments revealed that HtrA2 prevents the aggregation of amyloid β_{42}, a major element of neurotoxic deposits in brains of the Alzheimer's disease (AD) patients, keeping the peptide in the monomeric state (Kooistra et al., 2009). HtrA2 interacts with $A\beta_{40}$ and $A\beta_{42}$ but the peptides are not direct substrates for the protease (Park et al., 2004). It is sugested that HtrA2 could protect from the AD development due to its chaperone function. Liu et al. (2009) confirmed the interaction of HtrA2 with Aβ in neuronally differentiated human NT2N cells (clonal human neurons) and also in brain tissue from Tg2576 mice. HtrA2 binds preferentially to oligomeric Aβ, the most neurotoxic form of Aβ inside neural cells, via the PDZ domain of the protease. Moreover, the interaction attenuates the HtrA2 proapoptotic activity and prevents the neuronal death (Liu et al., 2009).

Homology

The HtrA2 protein is evolutionarily conserved among mammalian species.
At the amino acid level homology between human HtrA2 and its orthologs from oppossum, cow, rat, mouse and chimpanzee reaches 82%, 90%, 87%, 85% and 100%, respectively. The identity between HtrA2 and these orthologs reaches 88%, 92%, 91%, 89% and 100%, respectively.
At least three paralogs of human HtrA2 have been identified: HtrA1 (L56, ORF480, PRSS11, ARMD7), HtrA3 (PRSP) and HtrA4. HtrA2 shares the 75, 75 and 71% homology with HtrA1, HtrA3 and HtrA4, respectively. The identity between HtrA2 and its paralogs reaches 54, 52 and 49%, respectively.

Mutations

Germinal

Two heterozygous missense mutations in the HTRA2 gene have been identified in patients with sporadic form of Parkinson's disease (PD) in a German population (Strauss et al., 2005). A G421T mutation in exon 1 leading to a A141S substitution was found predominantly in PD patients and defined as a polymorphism associated with PD. A G1195A mutation in exon 7 resulting in a G399S substitution was identified exclusively in the PD patients. Both mutations caused a decrease of the HtrA2 proteolytic activity in vitro and affected morphology and function of mitochondria. Additionally, the G399S mutation caused an increased susceptibility to stress-induced cell death (Strauss et al., 2005). Further study revealed that neither the A141S mutation nor the G399S substitution were associated with the susceptibility to the PD development in a North American population (Simon-Sanchez and Singleton, 2008). Another PD-specific HTRA2 mutation in the PDZ domain, R404W was identified, in a mutation analysis of Belgian PD patients (Bogaerts et al., 2008a). Theoretically, this mutation should affect HtrA2 protease activity. Eight novel mutations in the HTRA2 coding region have been found: the non-synonymous W12C, P128L, F172V and A227S substitutions, and the synonymous V109V, L118L, R203R and L367L mutations. These changes were found in both the PD cases and healthy controls and did not show an association with the PD development (Simon-Sanchez and Singleton, 2008).

Implicated in

Various cancers

Note

Analysis of available microarray data indicated that expression of HTRA2 in different cancers varies according to tumor type (Chien et al., 2009). HTRA2 expression was up-regulated in lung adenocarcinoma, superficial or invasive transitional cell carcinoma of bladder, oligodendroglioma (brain) and squamous cell carcinoma of head and neck. HTRA2 was also up-regulated in B-cell acute lymphoblastic and T-cell lymphoblastic leukaemia compared to the acute myeloid leukaemia, in Wilm's tumors compared to normal fetal kidney or clear cell sarcoma, and in microsatellite unstable colorectal carcinoma compared to the microsatellite stable colorectal carcinoma. In contrast, a diminished expression of HTRA2 was observed in ovarian cancer, metastatic prostate cancer and adult male germ cell tumor. In breast cancer HTRA2 expression was reduced with the increasing tumor staging.

Oncogenesis

HtrA2 acts as a regulator of mitochondrial homeostasis

facilitating cell survival rather than cell death. However, under stressful conditions its function changes into proapoptotic. Since HtrA2 plays a crucial role in the induction of apoptosis there is an obvious link with cancer development because dysfunction of apoptosis facilitates neoplastic transformation. Disturbances in the HtrA2 proapoptotic activity may also contribute to metastasis since the implication of HtrA2 in anoikis has been reported. Several studies argue the involvement of HtrA2 in oncogenesis. However, variable expression of HTRA2 depending on cancer type complicates unambiguous definition of the HtrA2 role in carcinogenesis.

Gastric cancer

Note

Lee et al. (2003) showed that the reduction of the HTRA2 expression correlated with advanced gastric adenocarcinomas, irrespective of histologic subtype, in comparison to normal gastric mucosal cells. Immunohistochemistry results suggest that HtrA2 plays a role in the development of stomach cancer (Lee et al., 2003).

Ovarian cancer

Note

Work of Yang et al. (2005) on chemoresistance of ovarian cancer cells (A2780 and COC1) to cisplatin points to the HtrA2 protein level as a one of the key factors in response to the treatment. The cisplatin-induced increase of the cytosolic HtrA2 level was associated with the down-regulation of XIAP, activation of caspase-3 and apoptotic response in cisplatin-sensitive ovarian cancer cells, but not in resistant cells.

The HTRA2 mRNA level was reported to be down-regulated in ovarian tumors (most evidently in borderline tumors) (Narkiewicz et al., 2008) and the HtrA2 protein levels were significantly lower in endometrial cancer tissues compared to normal controls (Narkiewicz et al., 2009).

Prostate cancer

Note

Immunohistochemical analysis showed that HTRA2 was overexpressed in prostate cancer compared to the normal prostate and benign prostatic hyperplasia, and the overexpression correlated with prostate cancer differentiation. The semiquantitative RT-PCR assay showed a much higher expression of HTRA2 in the prostate cancer group compared to the benign prostatic hyperplasia group (Hu et al., 2006). Additional link between HTRA2 and prostate cancer (in cell lines PC3 and DU145) was provided by Zhu et al. (2010) who demonstrated a connection between HTRA2 and integrin alpha7 (ITGA7). ITGA7 acts as a proapoptotic factor and is down-regulated in prostate cancer. Yeast two-hybrid analysis revealed that the C-terminus of ITGA7 interacts with HtrA2 and it was shown that expression of ITGA7 increased the HtrA2 protease activity both in vitro and in vivo, whereas down-regulation of HtrA2 dramatically reduced cell death mediated by ITGA7. In addition, protease-null mutant HtrA2S306A expression blocked apoptosis induced by ITGA7.

Lymphoma and leukaemia

Note

Results of Okada et al. (2004), concerning BCR-ABL-positive human leukaemic cells (BV173 and K562) indicated HtrA2 as a caspase-independent, necrosis-like programmed cell death factor. They observed the mitochondrial release of HtrA2 into the cytosol of the cells treated with imatinib mesylate and, furthermore, serine protease inhibitors prevented the caspase-independent necrosis.

Work of Li et al. (2011) on HTRA2 expression using immunohistochemistry showed a weak and comparable expression in all normal lymph nodes, diffuse large B-cell lymphomas and small lymphocytic lymphomas, suggesting a rather minor role of HtrA2 in the regulation of apoptosis in these types of cancer. On the other hand, Baou et al. (2010) showed that cytosolic level of HtrA2 in chronic lymphocytic leukaemia cells increased after bortezomib treatment, suggesting HtrA2's role in the bortezomib-mediated caspase-dependent apoptosis.

Parkinson's disease (PD)

Note

Several single nucleotide polymorphisms (SNPs) of the HTRA2 gene have been identified and their relevance in PD has been studied.

The mouse mutation mnd2 resulting in the missense substitution S276C in the HtrA2 protease domain causes a phenotype resembling PD (Jones et al., 2003). In humans, genetic variation analyses have provided conflicting results regarding the involvement of the HTRA2 gene in PD. Results of Ross et al. (2008), Simón-Sánchez and Singleton (2008), Sutherland et al. (2009), Krüger et al. (2011) revealed no significant associations between the studied polymorphisms and PD, whereas studies of Strauss et al. (2005) and Bogaerts et al. (2008a, 2008b) did associate HTRA2 SNPs with PD. Westerlund et al. (2011) found a weak association of HtrA2 A141S with Alzheimer's disease.

The first connection between HtrA2 dysfunction and PD came from the study of Jones et al. (2003) on the motor deficient (mnd2) mutant mice. The mnd2 mutation, leading to neurodegeneration, muscle wasting, involution of the spleen and thymus and death by 40 days of age, was identified in the HTRA2 gene. Moreover, a neurodegenerative phenotype with parkinsonian features has been described in the HTRA2 knockout mice (Martins et al., 2004). A loss-of-HTRA2 study on the mouse model showed accumulation of unfolded proteins in mitochondria, a defective mitochondrial respiration and an enhanced production

of reactive oxygen species in the brain tissue cells (Moisoi et al., 2009). Study of Strauss et al. (2005) determined mutations (A141S - rs72470544, G399S - rs72470545) in the HTRA2 gene leading to a loss of or a reduced protease activity, respectively, in German PD patients. Immunohistochemistry revealed that both mutations induced mitochondrial dysfunction associated with the altered mitochondrial morphology. The A141S polymorphism was associated with PD ($p<0,05$) and G399S mutation was identified in four patients and was absent in healthy controls. Plun-Favreau et al. (2007) showed that point mutation in HTRA2 resulted in impairment of HtrA2 protease activity in PD patients carrying PTEN-induced kinase 1 (PINK1) mutations - mutations which were connected with the early onset parkinsonism. Later on, PINK1 was found to enhance HtrA2 activity by its phosphorylation and thus to participate in the maintenance of mitochondrial homeostasis (Whitworth et al., 2008). It should be noted that Yun et al. (2008) found that HtrA2 null mutants in Drosophila, in contrast to pink1 or parkin null mutants, do not show mitochondrial morphological defects. They questioned the role of HTRA2 as a component of the PINK1 pathway and an important player in PD pathogenesis. Several single nucleotide polymorphisms within HTRA2 gene have been tested for association with PD in large-scale studies. Study of Ross et al. (2008) on rs1183739, rs2241028, rs2231250, rs10779958 and rs72470544 (890 PD patients and 1479 controls from US, Ireland, Norway and Poland); of Simón-Sánchez and Singleton (2008) on rs2231248, rs2231249, rs2241027, rs2241028 and rs11538692 (644 PD patients and 828 controls from North America); of Sutherland et al. (2009) on rs1183739 (PD cases: 331 and controls: 296, Australia) and of Krüger et al. (2011) on rs1183739, rs2231250, rs2241028, rs10779958 and rs72470544 (large-scale genetic association study on total sample of 6378 PD patients and 8879 controls throughout Europe, North America, Asia and Australia) revealed no statistically significant associations for any of the SNPs with PD. This set of recent studies indicates that the role of HTRA2 in the development of PD remains to be clarified (De Castro et al., 2011), even though HtrA2 protein plays a protective role during stress in the mitochondria of healthy cells (Martins et al., 2004).

Disease

Parkinson's disease is a progressive neurodegenerative disorder of central nervous system and the most common movement disorder (about 1% of the population over 60 years of age). A pathological hallmark of PD is the presence of Lewy bodies and the loss of dopaminergic neurons in the substantia nigra pars compacta leading to a dopamine deficit in the striatum. Clinically, PD manifests with bradykinesia, hypokinesia, rigidity, resting tremor and postural instability, with an onset of symptoms occurring generally between the fifth and seventh decade of life. Patients may also develop autonomic dysfunction, cognitive changes, psychiatric symptoms, sensory complaints and sleep disturbances. A number of environmental factors and gene mutations (for a minority of cases) have been implicated in PD (Bogaerts et al., 2008a; Plun-Favreau et al., 2008; Winlklhofer and Haass, 2010; De Castro et al., 2011).

Alzheimer's disease (AD)

Note

The first association of HtrA2 with Alzheimer's disease (AD) was shown by a study, in which HtrA2 was identified as a presenilin-1 (PS1)-interacting factor in a yeast two-hybrid screen (Gray et al., 2000). PS1 is a catalytic subunit of gamma-secretase involved in amyloid beta-precursor (APP) processing and it is suggested that mutations in the gene encoding PS1 selectively elevate the levels of highly amyloidogenic peptide $A\beta_{42}$ and cause an increased death of neural cells by apoptosis and necrosis. The HtrA2-presenilin interactions were confirmed by Gupta et al. where the C-terminus of PS1 peptide has been shown to interact with HtrA2 and stimulate HtrA2 protease activity in vitro. Ectopic expression of PS1 potentiated HtrA2-induced cell death. These results suggested that PS1 may regulate the protease activity after its release from mitochondria during apoptosis (Gupta et al., 2004). Recently, association of HtrA2 with gamma-secretase and its positive effect on gamma-secretase activity in isolated mitochondria have been shown (Behbahani et al., 2010). Using yeast two-hybrid assays, Park et al. found that the amyloid beta-peptide (Aβ) also interacts with HtrA2. Although HtrA2 interacts with $A\beta_{40}$ and $A\beta_{42}$, the Aβ peptides do not serve as direct substrates for the protease. However, overproduction of HtrA2 in K269 cells reduced the Aβ levels up to 30 %. The function of HtrA2 as an inhibitor of Aβ oligomerization suggested a chaperone role for HtrA2 in the metabolism of intracellular Aβ in AD (Kooistra et al., 2009; Park et al., 2004). Liu et al. (2009) demonstrated that HtrA2 selectively interacts with oligomeric Aβ. The interaction protects neurons from the neurotoxic Aβ accumulation and also causes the reduction of the HtrA2 proapoptotic activity preventing death of neural cells. In addition, the proteins of APP family: APP, APLP1, APLP2 are direct substrates for HtrA2 in vitro (Park et al., 2006). Moreover, a novel function of HtrA2 as a regulator of APP metabolism through ER-associated degradation has been demonstrated (Huttunen et al., 2007). Furthermore, Ucf-101, an HtrA2 inhibitor, protects against cerebral ischemia/reperfusion injury in mice, providing neuroprotection in vivo (Su et al., 2009). Taken together, interactions between HtrA2 and Aβ, presenilin or APP suggest a possible link between HtrA2 and AD (Gupta et al., 2004; Park et al., 2006). Among many studies, HtrA2 has been suggested to be a

potential target in AD (reviewed by Bhuiyan and Fukunaga, 2009).

Disease

Alzheimer's disease is a progressive neurodegenerative disorder. AD is characterized by cognitive dysfunction, various behavioural and neuro-psychiatric disturbances and on cellular/ biochemical level by the deposition of extracellular plaques, which consist of amyloid beta (Aβ) peptides and intracellular neurofibrillary tangles. Major components of the senile plaques are $A\beta_{40}$ and $A\beta_{42}$ peptides generated from the COOH-terminal end of amyloid precursor protein (APP) by action of beta and gamma-secretases.

Huntington's disease (HD)

Note

Study of Inagaki et al. (2008) on rat primary neurons revealed a connection between the neuronal death and a selective down-regulation of HTRA2 gene by mutant huntingtin (htt) in striatal neurons. Furthermore, at the protein level both the full-length and the mature forms of HtrA2 were not affected in primary cortical or cerebellar neurons but were reduced in striatal neurons. These findings suggest a link between HTRA2 selective down-regulation and striatal neuron-specific pathology in HD.

Disease

Huntington's disease is one of neurodegenerative disorders manifested by unwanted choreatic movements, behavioural and psychiatric disturbances and dementia. Brains of HD patients are characterised by selective degeneration of medium-sized spiny neurons in the striatum and later on, in the disease progression, of cortical neurons. HD belongs to a family of polyglutamine disorders and is caused by an autosomal dominant mutation of Huntingtin (Htt) gene. CGG repeats in the DNA sequence of the Htt gene result in variably extended polyglutamine (polyQ) repeats in htt protein - repeats exceeding 35-40 are associated with HD.

Breakpoints

Note

No breakpoints described so far.

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