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Gene Section
Review

PRND (Prion Protein 2 (Dublet))

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Abstract

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

Identity

Other names: DOPPEL, DPL, PrPLP, dJ1068H6.4

HGNC (Hugo): PRND

Location: 20p13

Local order: PRND lies 27 kb downstream the human prion protein gene (PRNP). PRNP starts at 4702556 and ends at 4709106 bps.

Note: PRND and PRNP genes form the prion gene complex and are regulated by their own promoter. Doppel is an acronym derived from downstream prion protein-like gene (Moore et al., 2001). PRNP and PRND are believed to arise through duplication of a single ancestral gene (Mastrangelo and Westaway, 2001).

DNA/RNA

Note

The Prnd gene was originally identified in mice during DNA sequencing of the cosmid clone isolated from the I/LnJ inbred mice strain (Lee et al., 1998).

This gene was discovered in transgenic (Tg) mice where the Prnp gene was ablated ($Prnp^{0/0}$ mice strains) resulting in a diseased phenotype characterized by loss of Purkinje cells in the cerebellum.

Interestingly, Prnp deletion in these mouse lines resulted in the formation of a chimeric Prnd transcript under the control of the strong Prnp promoter. Thus, these studies have shown that only the ectopic expression of Dpl, rather than the absence of the Prnp gene, caused neurodegeneration (Li et al., 2000).

Description

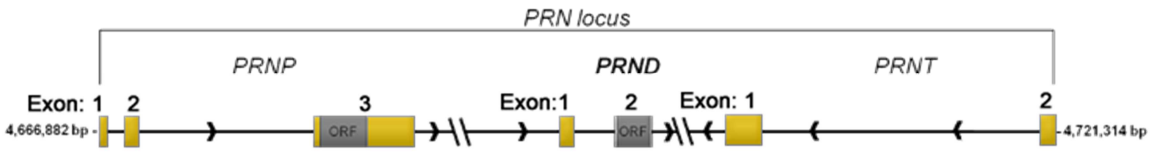
The PRND gene includes two exons separated by one intron. Exon 2 encodes for the Doppel protein.

Transcription

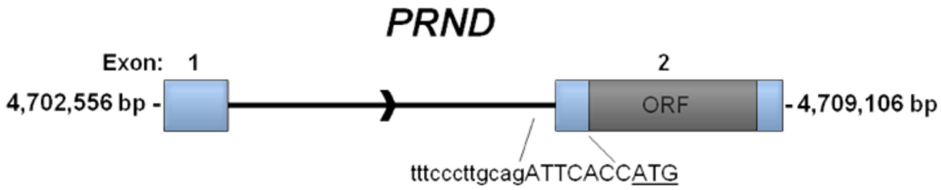
Prnd RNA transcription has been reported in different tissues of adult wild-type (WT) mice including testis, heart, spleen and skeletal muscle (Li et al., 2000). In neonatal mice up to 3 weeks, Prnd RNA has been detected in brain blood vessel endothelial cells (Li et al., 2000).

Pseudogene

Prnd pseudogenes have been identified in non-mammalian organisms as Anolis (lizard) and Xenopus (frog) (Harrison et al., 2010).



Schematic structural representation of the human PRN locus on chromosome 20p13 containing PRNP, PRND and the putative testis-specific prion protein (PRNT) genes.



Schematic representation of the PRND gene. Exon 1 starts at 4705556 bp and ends at 4702615 bp. Exon 2 containing the Doppel open reading frame (ORF) starts at 4705187 bp and ends at 4709106 bp. The sequence surrounding the splice acceptor site is shown with intronic nucleotides in lower case, exonic nucleotides in capital letters and Met start codon ATG underlined.

Protein

Note

Doppel tertiary structure has a fold similar to that of the cellular prion protein, PrP^C (encoded by PRNP or Prnp genes) although it shares approximately 25% of aminoacidic sequence identity with PrP^C.

Description

The immature form of human Doppel includes 176 residues with two N- and C-terminal signal peptides cleaved during protein maturation. The mature sequence includes 126 amino acids spanning from residues 27 to 152, with a molecular weight of approximately 14.5 kDa. Tryptic digestion and mass spectroscopy studies have identified two distinct disulfide bridges (Cys109-Cys143 and Cys95-Cys148) which strongly stabilize the Doppel folding (Baillod et al., 2013; Silverman et al., 2000; Whyte et al., 2003). PNGase F digestion and immunoblots have reported two N-linked glycosylation sites at codons 99 and 111. The GPI anchor targets the protein at the extracellular membrane. NMR structures of recombinant human and mouse Dopple have been solved (Luhrs et al., 2003; Mo et al., 2001). The NMR structures of the N-terminal murine and ovine signal peptides (residues 1-30) have also been determined (Papadopoulos et al., 2006). The human Doppel NMR structure features a short flexible N-terminal segment comprising residues 24-51 and a globular domain including four α-helices (α1: residues 72-80; $\alpha2^a$: residues 101-115; $\alpha2^b$: residues 117-121; α3: residues 127-141) and a short two-stranded anti-parallel β-sheet (β1: residues 58-60; β2: residues 88-90) (Luhrs et al., 2003).

Expression

Under physiological conditions Doppel is mostly expressed in testis and, in particular, in spermatozoa and Sertoli cells (Behrens et al., 2002; Peoc'h et al., 2002). Additionally, Doppel is expressed with PrP^C in spleen cells, notably B lymphocytes, granulocytes and dendritic cells (Cordier-Dirikoc et al., 2008).

Localisation

Doppel is attached to the cell membrane through its GPI anchor (Silverman et al., 2000). A study has shown Doppel localization in detergent-resistant membranes or lipid rafts (Caputo et al., 2010).

Function

The Doppel expression in spermatozoa and Sertoli cells infers a role in spermatogenesis. Male Tg mice knock-out for Prnd were sterile, clearly indicating that Doppel plays a role in male reproduction as critical regulator of spermatogenesis and sperm-egg interaction (Behrens et al., 2002). Doppel may enhance in vitro ovine spermatozoa fertilizing ability (Pimenta et al., 2012).

Doppel has been implicated in early testis differentiation (Kocer et al., 2007). The detection of Prnd mRNA in brain blood vessel endothelial cells might indicate a possible role in the development of brain blood vessels (Li et al., 2000). The observation that Doppel is expressed with PrP^C in B lymphocytes, granulocytes and dendritic cells argues for a role in cell-cell interaction in the immunosystem (Cordier-Dirikoc et al., 2008). Several evidence showed that Doppel is able to coordinate in vitro the binding of copper ions with high affinity (Cereghetti et al., 2004; La Mendola et al., 2010; Qin et al., 2003).

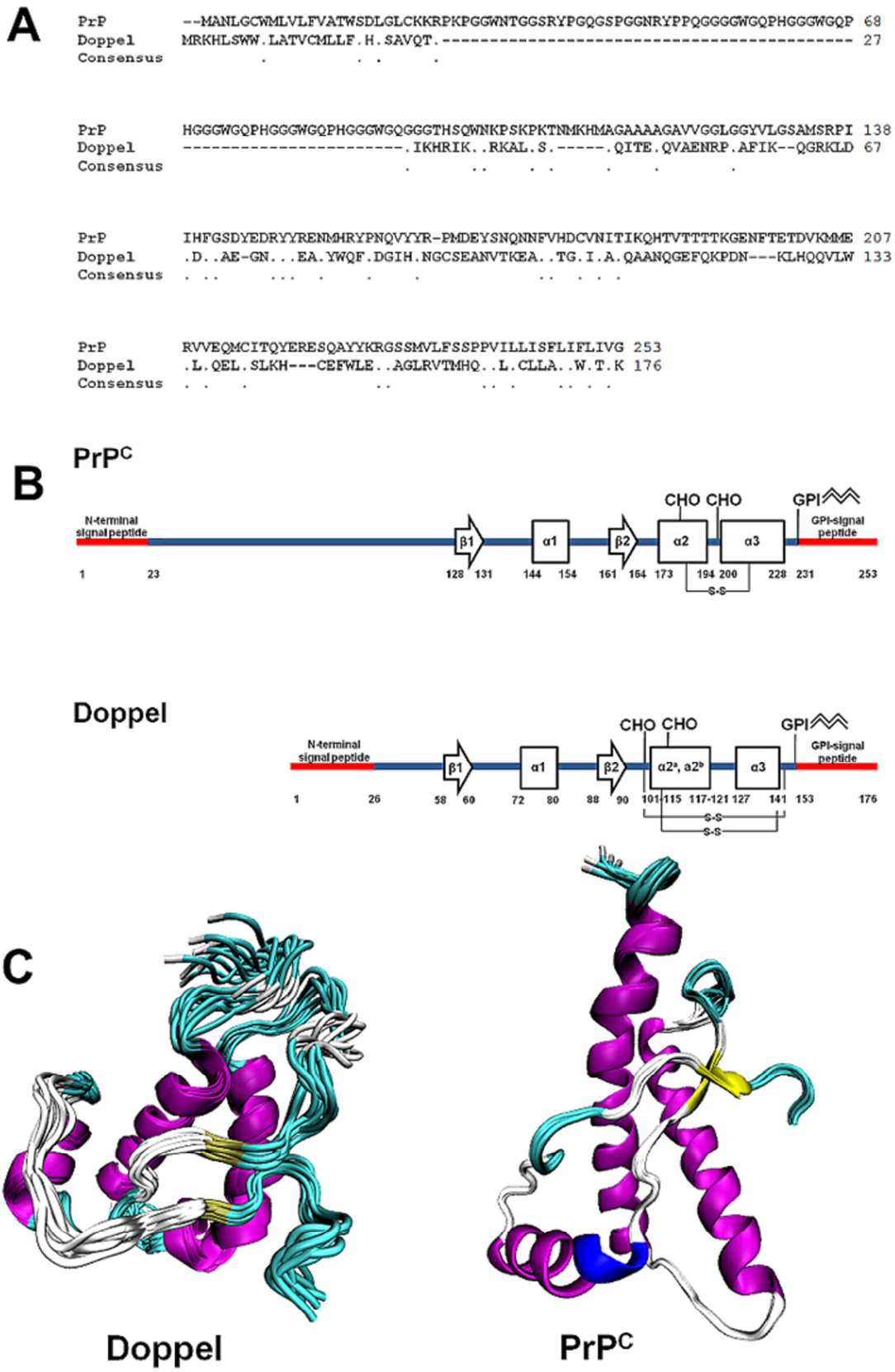
Mutations

Note

Different polymorphic variants have been identified in PRND. The effect of polymorphisms in Doppel function and their implication in the diseases have not been fully clarified.

Germinal

S6I, S22P, T26P, H31R, P56L, F70L, L149S, T174M (Clark et al., 2003; Moore et al., 1999; Peoc'h et al., 2000; Schroder et al., 2001).



A) Primary sequence alignment between human PrP^C (GenBank: BAG32277.1) and human Doppel (NCBI Reference Sequence: NP_036541.2). **B)** Secondary structure motives of human PrP^C and Doppel. Highlighted: signal peptides, N-linked glycosylation sites (CHO), disulfide bridges (S-S) and Glycosylphosphatidylinisotol (GPI) anchor. **C)** Tertiary NMR structures of Doppel (pdb id 1LG4) and PrP^C (2LSB).

Implicated in

Ectopic Doppel expression associated with Purkinje cell neurodegeneration in transgenic mouse models.

Note

Beside its role in male reproductive system, Doppel has attracted interest for its neurotoxic properties when ectopically expressed in the brain of Tg mice knock-out for the prion protein gene ($Prnp^{0/0}$ mice). In these mice, denoted as Ngsk $PrP^{-/-}$, the Doppel-encoding exon was expressed as chimeric mRNA due to the intergenic splicing taking place between Prnp and Prnd.

As a result, Prnd became abnormally regulated under the control of Prnp promoter and ectopically expressed in the brain and, in particular, in neurons and glial cells (Li et al., 2000).

Similar non-physiological Doppel expression was reported in other Tg mouse lines knock-out for Prnp such as Rcm0 and Zrch mice (Moore et al., 2001; Rossi et al., 2001).

Doppel expression in the brain is neurotoxic and causes Purkinje cell degeneration in these mouse models. Doppel neurotoxicity is antagonized by the PrP^{C} N-terminal domain (Atarashi et al., 2003; Yamaguchi et al., 2004).

The neuroprotective PrP^{C} role against ectopic Doppel expression has been reported also in human neuronal SH-SY5Y cells (Li et al., 2009) confirming the dominant-negative effects of the PrP^{C} N-terminal region (Yoshikawa et al., 2008). The molecular mechanisms leading to Doppel-induced neurodegeneration in Purkinje and granular cells are still controversial.

An earlier study has reported that the chimeric form of Doppel fused to a Fc domain binds specifically granule cells and causes neurodegeneration, raising the possibility that these specific cells expressed a still unidentified protein that mediates the Doppel-induced neurotoxicity (Legname et al., 2002). Oxidative stress may play a role in Doppel-induced neuronal death since NOS activity is induced by Doppel in vitro and in vivo (Cui et al., 2003; Wong et al., 2001).

Two independent groups have reported that BAX contributes to Doppel-induced apoptosis (Didonna et al., 2012; Heitz et al., 2007) and that BCL-2 antagonizes Doppel neurotoxicity (Heitz et al., 2008).

Another work has observed that ectopic Doppel expression in the brain elicits neurodegeneration through the binding of two metalloproteinase namely the alpha-1-inhibitor-3 (α1I3) and the alpha-2-macroglobin (α2M) (Benvegnu et al., 2009).

Abnormal Doppel expression levels in human astrocytomas and other non-glial brain tumor specimens

Note

Doppel is aberrantly expressed in astrocytic tumors where it displays cytoplasmic, nuclear and lysosomal localization and molecular properties (i.e. altered glycosilation pattern) different from Doppel as normally expressed in testis (Azzalin et al., 2006; Azzalin et al., 2008; Comincini et al., 2006; Comincini et al., 2004; Comincini et al., 2007; Rognoni et al., 2010; Sbalchiero et al., 2008).

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