**NEW PROTEINS WITH PRION-LIKE DOMAINS INVOLVED IN NEURODEGENERATIVE DISEASE**

**What is prion and how can we study them?**

Prions are self-templating protein conformers that are naturally spread within an individual, between individuals, and even between different species and promote phenotypic change.

Proteins with prion-like domains (PrLD) resemble to the ones found in yeast but preclude prionogenesis and promote progressive neurodegenerative disorders as a consequence of protein misfolding and aggregation.

**Bioinformatic tools - PrionScan and PAPA algorithms**

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<th>hnRNPA1</th>
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PrionScan and PAPA (prion aggregation prediction algorithm) are two predictive PrLD algorithms which allowed scoring protein sequences according to their likelihood of being prions. They agree that an intrinsically disordered glutamine/asparagine (Q/N) rich prion forming domain (PFD) drives prion formation.

hnRNPA1 and Med12 have high score although only PrLD-hnRNPA1 has been proved experimentally with exome sequencing of two families with neurodegenerative diseases. Here a hypothesis for Med12 role in neurodegeneration is proposed.

**hnRNPA1 - Proved role in neurodegeneration**

hnRNPs comprise a multifunctional family of RNA-binding proteins. They participate in pre-mRNA processing such as splicing and are important determinants of mRNA export, localization, translation and stability.

**Mutations** greatly accelerate hnR1A1 ability to aggregate and form amyloid fibers in both hnRNPA1 isoforms.

Amyotrophic lateral sclerosis

- D262N in hnRNPA1
- D314N in hnRNPA1-B

Multisystem proteinopathy

- D262V in hnRNPA1
- D314V in hnRNPA1-B

The critical rate-limiting step in fibrillation is nucleation. The disease mutations shorten the lag phase and enhance fibrillation while the WT protein remained in lag phase. Sequence alignment of hnRNPA1 orthologues show evolutionary conservation of the mutated asparagine and surrounding residues, which means is an important residue to its molecular function.

**Med 12 – Hypothetical role in neurodegeneration**

Med12 is one of the proteins of Mediator, a complex which serves as a bridge between DNA-binding transcription factors, G9a histone methyltransferase, and RNA polymerase II. It is composed of 4 different subunits: head, middle, tail and CDK8.

Mediator regulates transcriptional activation in the S-Mediator active conformation, whereas the association of separable kinase CDK8 module forms the L-Mediator repressive conformation blocking the interaction with RNA polymerase II. Med12 is found in this CDK8 module.

Interestingly, genome-wide analyses showed profound impact of Med12 variation on four members of HSP70 heat shock protein expression in HEK293 cells in vitro. Heat shock proteins (HSP) are highly conserved molecular chaperones that recognize and selectively bind proteins to form stable complexes to prevent misfolding and aggregation.

**References:**
