1. Introduction:
In recent years, neurodegenerative diseases are related to prion-like aggregates formation. This work discusses how to predict prion-like domains from protein amino acidic composition and then, use bioninformatic algorithms to select a couple of proteins and search in bibliography what are the knowledge about them and their relation with disease or relate them to disease which could be involved with.

2. Prion-like domains and their prediction:
A prion is an infectious protein or an infectious protein fragment, called prion-like domain capable to make aggregates involved in transmissible neurodegenerative diseases. These are low-complexity regions, Q, N and hydrophobic amino acids rich regions, and also lack in charges and P. Their conservation suggest they can also accomplish important functions inside the cell, like transcription, translation or non-membrane cell compartments formation.

Various investigation groups have develop specific algorithms that allow differentiate these regions forming prionic aggregates form those sequences which generates non-prion-like amyloid aggregates. The algorithms used in this work were PAPA and PrionScan. Both predict these prion-like domains from the compositional protein characteristic of complete proteomes. We started from 824 human proteins previously selected and then we compare the results obtained in the follow graphics (Figures 1 and 2).

3. Correlation graphs:

4. Correlation score and position discussion:
The main difference between these algorithms falls into LO values for each amino acid. Table 1 shows both libraries. For PAPA, the most important amino acids are the hydrophobic, inclusive aromatics, whereas for PrionScan most important amino acids are Q and N. So, PAPA predicts regions that form non-prion-like aggregates like prionic domains, results that are false positives. Otherwise, PrionScan cannot detect these regions as prion-like domains but these that have elevate contain in Q/N. In other words, PAPA is an algorithm with higher sensibility, but detects more false positives, and is less precise. However, PrionScan has lower sensibility but detects less false positives, so it is more precise. Despite these differences, I have chose two proteins, TDP43 and MED15 (punctuations shown in Table 2).

5. TDP43:
TDP43 is a 414 residues and 43 kDa human protein that belongs to TARDBP family. This protein is capable to bind DNA and RNA and is involved in very important functions in all the cells like general RNA regulation, alternative splicing, RNA nuclear to cytoplasm exportation, transcription and translation. In neurons, this protein has specific functions like RNA and microRNA transport from neuronal soma to axonal terminal. There are evidences which prove TDP43 prion-like domain has functional implications. TDP43 are involved in amyotrophic lateral sclerosis (ALS) and fronto-temporal lobar disease (FTLD). In both, TDP43 forms prionic-aggregates which can cause toxicity and neuron death. TDP43 aggregates contain truncated-TDP43 (corresponding to C-terminus fragments (CTF)) fragments by caspase-3 and full-length TDP43. Aggregates also are hyperphosphorylated and ubiquitinated. Despite all of these, prion-like possibility of initiation, and their implications with diseases still unclear.

6. MED15:
MED15 is a 788 residues and 87 kDa human protein. MED15 belongs to MED family, and are one of RNA polymerase II complex mediator members. This complex has a very important function: to transmit information DNA to RNA polymerase II. MED15 has been involved in diseases like D’George syndrome, obesity, type-2 diabetes and cardiovascular diseases. Despite the implication in these implications, there still are not evidences of MED15-aggregation in these diseases. An hypothetical evidence of prion-like current function is this domain is localized in the middle of ARC105 domain, which is essential to DNA-protein and protein-binding. The prion-like domain presence and conservation between species may think this domain could be involved into forming these interactions. Mutations and deletions could increase prion aggregates formation and could disregulate the cell translation system.

7. Conclusions:
Scientist try to reveal these possible prion-like domains using algorithms. The main problem is to find the correct combinations of punctuations, because each amino acid has different contribution in prionic aggregates. In order to obtain better predictions, the aim is to design an algorithm that gives the correct weight to each amino acid considering compositional features of these prion-like regions.

TDP43 has clear evidence to be involved into prion aggregates formation. The investigation has to be focus on find the initiation aggregation mechanism and aggregates implication in disease. MED15 has to be investigated in order to relate it with diseases with prionic aggregates presence.

Prion-like domains could be a good tool in cell interacting mechanisms and also in adaptive processes, where could proportionate adaptive advantages. These could be good reasons to their conservation along the evolution of organism. But the ability and the implication in neurodegenerative and other types of diseases is the main point of the issue which has to follow under investigation.

References: