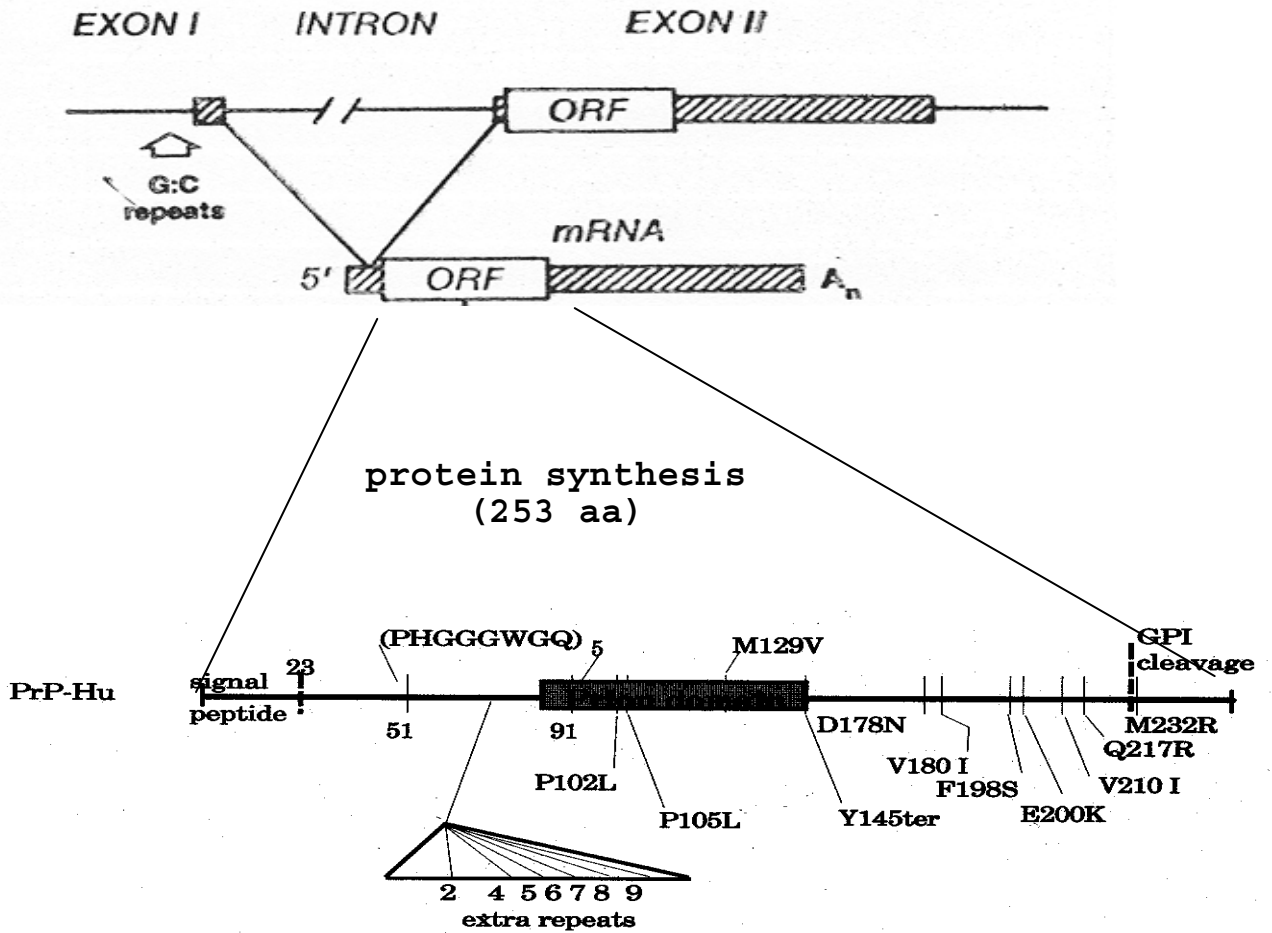


## PRIONS

The human prion protein gene and its gene product



- I. The Prion Gene - Prnp
  - A. Located at 20p12 - human
  - B. All known mammalian Prnp's have a single ORF
    1. exon(s)1 (and 2) contain 5'-UTR
    2. exon 2 (or 3) contains ORF & 3'-UTR
    3. The ORF is 759 bp
    4. Long 3'-UTR
  - C. intron - 15 kb (with many SINEs, LINEs and retroposons)
  - D. No TATAAT box - a GC rich region
  - E. See: Genbank AN NM000311
  - F. See also: Prusiner, SB. The Prion Diseases. Sci. Am., Jan., 1995.

### II. The Prion Protein

- A. The normal protein - Prp<sup>c</sup>
  1. Membrane-bound neuronal protein

2. Function unknown - Cu-binding protein
  3. Made as a 253 aa peptide - several post-translational modifications
    - a. Signal sequence is recognized & removed first 23 aa
    - b. Peptide is removed from c-terminus as GPI is added - last 21 aa
    - c. Glycans added to two asn - 181 & 197
    - d. One disulfide bond formed cys<sub>179</sub>-cys<sub>214</sub>
  4. Octarepeat: PHGGGWGQ - five times: 51-91
  5. The Prion Domain: 85-150 ??
    - a. Highly conserved among all mammals
    - b. Probably responsible for conformational change to PrP<sup>sc</sup>.
  6. Polymorphisms:
    - a. Less one repeat: -8aa @ repeat site
    - b. M129V
- B. The Altered Prion Protein - PrP<sup>sc</sup>
1. fCJD - 10% of all cases
    - a. Extra repeats - esp. 48 aa insertion - Many families
    - b. E200K - Lybian Jews, others
    - c. D178N - (with V at 129) - Many families
    - d. V210I - classic fCJD
    - e. Others: Y145ter, F198S, etc.
  2. GSS - Most cases are inherited
    - a. P102L - Many cases
    - b. A117V - A dementing form of GSS
    - c. L105P
  3. FFI - Inherited, with sleep disorder - has thalamic involvement
    - a. D178N - (with M at 129)
    - b. Others ?