**Supplemental Table 2:** Summary of evidences presented in support of evolutionary descent of PrP gene family from ZIP metal ion transport ancestor gene.

| Evidence Category | | Description of Evidences |
|---|---|---|
| *1. Sequence* | a. | ZIP10 constitutes the only non-prion gene hit by SCOP "prion-like" HMM (out of 120,000 entries in LOCATE human-mouse protein database). |
| | b. | COMPASS profile-profile analysis passed homology E-value threshold and confirmed that similarity of PL domain sequences is not merely restricted to spurious outliers. |
| | c. | The GPI-attachment sequence of prion gene sequences shows remarkable sequence identity/similarity with the TM1 domain found in ZIPs. Precedents exist for the transformation of a transmembrane sequence into a signal peptide for GPI anchor attachment. |
| | d. | An additional pair of ZIP and prion gene sequences (zebrafish ZIP5 / pufferfish Sho2) exhibits a degree of sequence identity/similarity which falls on the significance threshold indicating homology. |
| | e. | ZIP genes contain histidine-rich repeat motifs reminiscent of octarepeats in prion sequences. |
| | f. | A zebrafish PrP sequence has been documented which shares the presence of N-terminal $[HX]_n$ clusters with ZIPs. |
| *2. Structure* | a. | A common distance of cysteine-flanked core domains to membrane attachment sites is observed in both prion and ZIP protein families. |
| | b. | Precedents of protein families exist with individual members employing transmembrane domains or GPI anchors for membrane attachment. |
| | c. | A systematic attempt to thread ZIPs 5/6/10 to any protein structure in the PDB led to the independent assignment of the prion fold. |
| | d. | The prion protein structures are the only fold templates onto which ZIP sequences can be threaded with scores that pass the threshold for significant homology. |
| | e. | ZIPs 5/6/10 are expected to display dichotomy of disordered N-terminal sequences and globular PL domains, reminiscent of prion proteins. |
| *3. Function* | a. | Consistent with multiple lines of evidence suggesting that proteins harboring the prion fold can bind to each other, ZIP proteins co-purified with prion proteins in this study. |
| | b. | While many proteins are known to bind divalent cations, PrP and ZIPs belong to a small group of proteins known to capture divalent cations at multiple binding sites embedded within disordered extracellular domains. |
| | c. | Both the prion protein and ZIPs 5/6/10 have been shown to transport zinc ions across the plasma membrane. |
| | d. | ZIP6 and PrP knockouts have been shown to display a rare common phenotype in zebrafish (inhibition of gastrulation / altered E-cadherin expression). |
| *4. Localization* | a. | ZIPs 5/6/10 and prion proteins share localization to the plasma membrane. |
| | b. | ZIPs 5/6/10 display common orientation of shared sequence motifs with regard to the plasma membrane. |
| | c. | Predominant tissues of expression of ZIPs 5/6/10 are reminiscent of PrP/Sho/Dpl gene expression profiles. |
| *5. Phylogenetics* | a. | Comparison of orthologous ZIP and prion sequences indicates divergent sequence evolution consistent with phylogenetic relationships. |
| | b. | ZIPs 6/10 identified to bind to members of mammalian prion protein family populate a common phylogenetic branch and represent the subset of mouse ZIPs (out of fourteen ZIP paralogs) which objectively display the strongest sequence similarity to prion gene sequences. |
| | c. | A simple and plausible model for the emergence of the prion gene family in Chordata exists. |