

Gerstmann-Straussler-Scheinker disease: a rare subgroup of prion diseases

by

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ABSTRACT

Prion diseases (PrD) or Transmissible Spongiform Encephalopathies (TSE) are a rare form of neurodegenerative disease. They can emerge as sporadic, infectious, or familial, and are characterized by accumulation of misfolded prion proteins (PrP) as amyloid deposits and spongiform degeneration of CNS tissue. PrD mimic viruses, but are propagated through protein-to-protein interaction. An extremely rare form of PrD known as GSS is brought on by a germline mutation in PRNP, the gene that codes for normal cellular PrP. Its clinical presentation is that of ataxia at onset, followed by dementia in the final stage. To date, there is no known cure or prevention for GSS or any other PrD.

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1. Prion Disease

Prion diseases (PrD), often collectively termed Transmissible Spongiform Encephalopathies (TSE), are a rare family of fatal neurodegenerative diseases, characterized pathologically by the presence of vacuolar degeneration of gray matter and prion protein (PrP) amyloidosis [1][2]. Five subgroups of prion disease affecting humans include Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob disease (vCJD), fatal familial insomnia (FFI), Gerstmann-Straussler-Scheinker disease (GSS), and kuru. The discovery that PrD manifest in humans as predominantly sporadic, but also infectious or familial, raised the question of how a disease can be both genetic and infectious [4]. Once thought to originate

from 'slow viruses' due to the prolonged incubation time of several months to years, it is now known that propagation of PrD involve vectors that are devoid of nucleic acid [2]. The infectious particle responsible for the transmission of PrD was identified in 1982, and shown to be entirely composed of a proteinase K resistant 27-30 kDa protein, known as PrP²⁷⁻³⁰ [3]. In order to set apart this infectious particle from others, such as viruses, it was designated a 'prion' which was "a contraction of *proteinaceous* and *infectious*" [2].

The main concept of PrD involves the post translational modification of normal cellular prion protein (PrP^c) to that of a mutant prion protein (PrP^{sc}). These misfolded PrP^{sc} accumulate in CNS tissue as amyloid

deposits and are accompanied by significant neurodegenerative effects [5]. The death of neuronal tissue has been attributed not to the loss of function of PrP^c, because its function remains largely unknown, but to the neurotoxic properties of PrP^{sc} [7]. The amyloid fibrils that aggregate in the CNS of patients with PrD have been shown to have the ability to form ion channels that interact with the lipid membranes of selective neuronal cells. These channels, along with the toxic properties of PrP^{sc}, aid in the induction of apoptosis and cell death [8].

2. The Prion Protein

Normal cellular prion protein (PrP^c) is a host-encoded protein that is modified in the endoplasmic reticulum to produce a 208 amino acid strand. It then passes to the Golgi apparatus where it is trimmed and modified before being exported to the cell surface. PrP^c has two distinct domains. The C-terminal domain, which is largely stable and structured, contains 3 α -helices stabilized by a disulfide bridge, a phosphatidylinositol glycolipid (GPI) serving to anchor it to the plasma membrane, two asparagine-linked oligosaccharides, and a protein X binding site. Protein X is thought to be a molecular chaperone that, when binded, lowers the activation energy of the transformation from PrP^c to PrP^{sc}. The N-terminal domain is largely unstructured and exists as a random coil. It is this domain that plays a significant role in the propagation of PrD. When PrP^c comes in contact with infectious PrP^{sc}, its random unstructured N-terminal domain is largely converted to B-sheet, transforming it from PrP^c to PrP^{sc}. The secondary structure of PrP^c is 43% α -helical and 3% B-sheet, whereas the mutant PrP^{sc} is very different, being mainly comprised of 43% B-sheet and only 30% α -helix [5]. This structural alteration gives PrP^{sc} new biochemical and biophysical properties. PrP^c is largely α -

helical, sensitive to digestion by proteases and detergent soluble [fig 1].

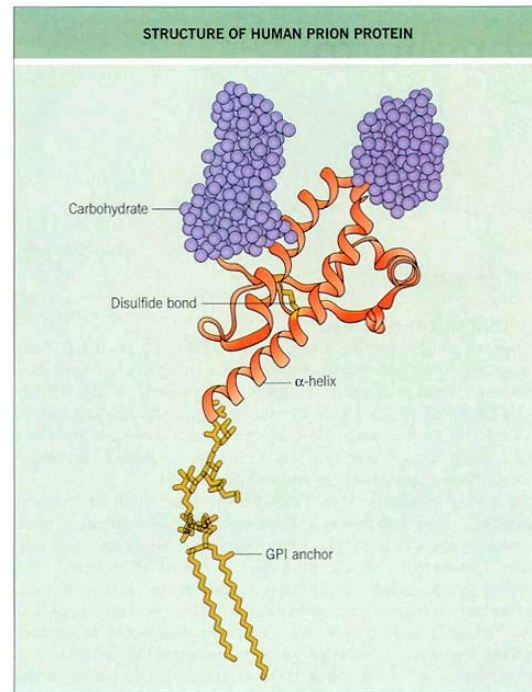


Figure 1. A representation of a normal cellular prion protein (PrP^c). Pictured are the positions of the 3 α -helices, stabilized by a disulfide bridge, a phosphatidylinositol glycolipid (GPI) that anchors it to the plasma membrane, two asparagine-linked oligosaccharides. It is viewed from the position of the protein X binding site. Protein X is thought to be a molecular chaperone that, when binded, lowers the activation energy of the transformation from PrP^c to PrP^{sc}.

PrP^{sc} exhibits markedly different characteristics, in that its secondary structure is largely B-sheet, it is partially protease resistant, insoluble in detergents, and has the tendency to aggregate into amyloid fibrils. It has been shown that amyloid fibrils in neuronal tissue are predominantly composed of B-sheet, therefore absence of random coil and presence of B-sheet would account for protease resistance and tendency to form amyloid fibrils [6].

3. The PRNP gene

PrP^c is encoded by a gene on the short arm of chromosome 20, designated PRNP. More

than 25 point mutations and insertions of PRNP have been identified and associated with the genetic forms of PrD.

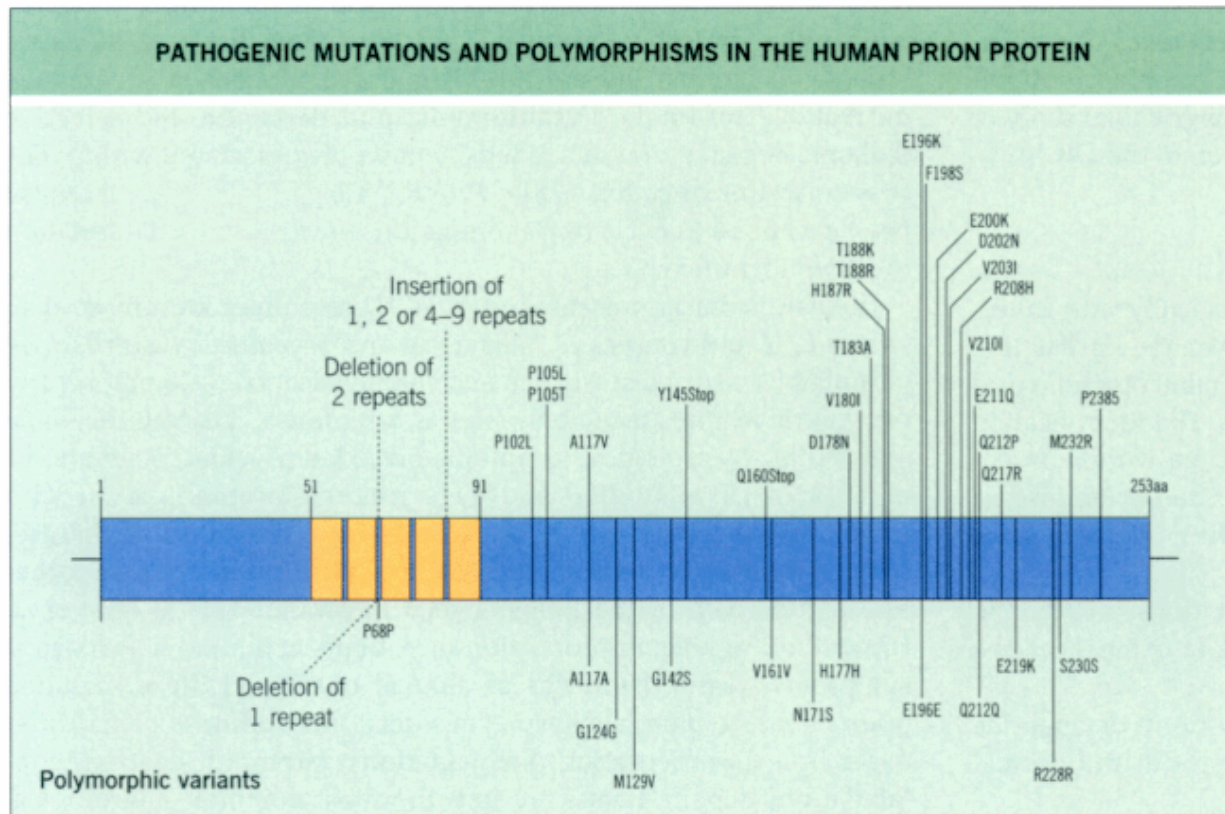


Figure 26-3 Pathogenic mutations and polymorphisms in the human prion protein. The pathogenic mutations associated with human prion disease are shown above the PrP coding sequence. These consist of 1, 2 or 4–9 octapeptide repeat insertions within the octarepeat region between codons 51 and 91, a deletion of 2 octapeptide repeats; and various point mutations causing missense amino acid substitutions. Point mutations are designated by the wild-type amino acid preceding the codon number, followed by the mutant residue, using single-letter amino acid conventions. Polymorphic variants are shown below the PrP coding sequence. Deletion of one octapeptide repeat is not associated with disease.

Each mutation causes a subtle difference in PrP structure that destabilizes it, predisposing it to assume a structural conformation different than that of PrP^C. The different conformations of PrP are each associated with different clinical and pathological phenotypes. Knock-out mice (mice genetically engineered lacking the PRNP gene) designated PRNP^{0/0} were inoculated with PrP^{Sc}, sacrificed and examined at specific intervals. Except for residual infectivity, no evidence of PrD was found in the brains, further supporting the concept that PrD is propagated on a protein-to-protein basis [9].

4. GSS

While many of the other PrD are classified as sporadic, infectious and familial, GSS is shown to originate solely from a genetic mutation. It is an extremely rare PrD, emerging in one to ten out of every 100 million people worldwide [5]. To date, only 56 families affected by this disease have been identified and studied [1]. GSS is inherited in an autosomal dominant fashion, implying that the progeny of an infected individual are at a 50% risk of developing the disease. The classic phenotype of GSS is clinically presented as the development of ataxia, with late onset dementia, as well as several other psychiatric and cognitive issues [5].

Pathologically, the brains of GSS patients have been found to have atrophy of the cerebrum and cerebellum, with extensive amyloid deposits, located primarily in the cerebellum. These deposits are composed of highly truncated 7 kDa PrP peptides, which are markedly shorter than the 20 kDa peptides composing the amyloid fibrils in other forms of PrD. This suggests a structural difference in the PrP^{Sc} of GSS patients [10].

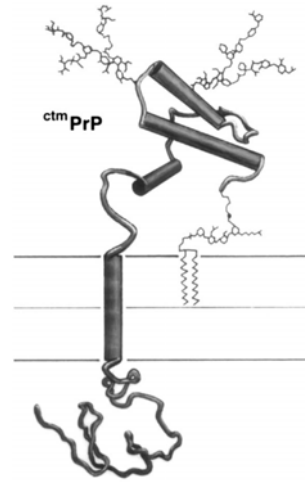


Figure 3. One possible structure of the transmembrane form of PrP found in GSS patients. This protein assumes a pathologic position on the cell surface, where the normally unstructured and free floating N-terminus is embedded in the plasma membrane. The ctmPrP is now anchored by the GPI on the C-terminus, and an embedded, transmembrane N-terminus. After protease digestion, a 7 kDa, protease resistant peptide remains. This peptide exhibits N and C-terminal truncated ends, as opposed to simply an N-truncated end which is found in other forms of PrD [2].

10 point mutations and insertions of PRNP have been identified and associated with the development of GSS. Each of these mutations code for a transmembrane form of PrP^{Sc}, designated ctmPrP. This protein assumes a pathologic position on the cell surface, where the normally unstructured and free floating N-terminus is embedded in the plasma membrane. The ctmPrP is now anchored by the GPI on the C-terminus, and an embedded, transmembrane N-terminus. After protease digestion, a 7 kDa, protease resistant peptide remains. This peptide spans from residues 81-82 to 144-153 of PrP [8], and exhibits N and C-terminal truncated ends, as opposed to simply an N-truncated end which is found in other forms of PrD [2]. The presence of this specific peptide is also associated with increase microviscosity in plasma membranes of neuronal cell

cultures. An increase in the microviscosity may alter membrane homeostasis and play a large role in the initiation and propagation of apoptosis and cell death [6].

5. Conclusion

In order to effectively treat PrD such as GSS, the clinician must first be able to accurately diagnose the disorder. PrD are difficult to identify and are often misdiagnosed as psychiatric disorders, Parkinson and Alzheimer's related illnesses, or ALS. The diagnosis of a PrD is based primarily on clinical symptoms and the course of the disease, as well as a thorough family history when an inherited form is suspected. To further confirm the presence of a PrD, CSF must be collected, or a biopsy of brain tissue after the patient has died must be collected. New and less invasive diagnostic tools are becoming available that have both high sensitivity and specificity. They penetrate the blood-brain barrier and allow clinicians to quickly identify amyloid deposits using PET. Rapid clearance is seen with no apparent deleterious effects [11].

To date, there is no known cure or intervention for GSS or any PrD. Several drugs have been screened and tested in various laboratory settings involving cultures and rodent models. Some of these drugs have shown promising curative potential, but have since shown much lower promise in other models [5]

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