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Molecular Genetics of Gerstmann-Sträussler-Scheinker Disease and Creutzfeld-Jakob Disease

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Abstract

Prion diseases are a group of transmissible neurodegenerative disorders associated with the misfolded form of the prion protein, PrP^{Sc}. The latter isoform is derived by conformational conversion of the normal prion protein, PrP^{c}. The gene encoding the prion protein is highly conserved among species. There are several distinct types of prion diseases in humans: kuru, Creutzfeldt - Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS) and Fatal Familial Insomnia (FFI) and its sporadic analogue, fatal sporadic insomnia. While human prion diseases are mostly sporadic, some 15% of CJD and all cases of GSS are hereditary disorders caused by mutations in the PRNP gene. There are two major types of mutations in *PRNP*: point mutations leading to amino acid substitutions and mutations leading to expansions of the octapeptide repeat region within the N-terminal part of the prion protein. This review describes different types of familial prion diseases linked to specific polymorphisms and mutation in *PRNP*.

Keywords: Prion diseases; Familial prion diseases; Creutzfeldt - jakob disease; Gerstmann-straussler-scheinker disease

Key Concepts

- Prion diseases are associated with the conformational conversion of a normal prion protein (PrP^{C}) into a misfolded form, PrP^{Sc}
- While the majority of CJD cases are sporadic, there are also familial forms
- All cases of GSS are hereditary
- Familial prion disease are caused by mutations in the gene encoding the prion protein

Introduction

Prion diseases, or Transmissible Spongiform Encephalopathies (TSEs), are a group of neurodegenerative disorders which include kuru, Creutzfeldt-Jakob Disease (CJD), Gerstmann-Sträussler-Scheinker Disease (GSS), and Fatal Familial Insomnia (FFI) and its sporadic analogue, fatal sporadic insomnia, in humans; natural scrapie in sheep and goats; Bovine Spongiform Encephalopathy (BSE) in cattle; Chronic Wasting Disease (CWD) in cervids; and Transmissible Mink Encephalopathy (TME) in ranch-reared mink. Variable Protease-Sensitive Prionopathy (VPSP) is a new disease described recently by Gambetti et al. [1] the majority of human prion diseases are sporadic, but there are also familial forms. Some of the latter were recognized long before the era of the 'protein-only' model of prion diseases and molecular genetics [2], as exemplified by the famous case of a disease in the Backer family [3].

Nomenclature

The normal form of the prion protein is known as PrP^{c} (c, from "cellular"). The misfolded, disease-associated isoform is typically denoted PrP^{Sc} (Sc, from scrapie, a prion disease of sheep). The PrP^{Sc} isoform has been classically considered equivalent to the aggregated form of the prion protein that is partially resistant to proteinase K (PK) digestion [1]. However, the situation is complicated by recent data showing that there may also be disease-associated forms of the prion protein that are susceptible to proteolytic degradation. Nevertheless, it is convenient to classify different forms of prion diseases according to the presence of particular types of PrP^{Sc} aggregates as defined by the PK digestion pattern.

Prp, Its Gene PRNP, and the "Prion Hypothesis"

PrP^{c} is encoded by a gene mapped to chromosome 20 in humans and chromosome 2 in mice [4]. The gene (*PRNP* in humans) is ubiquitous and highly conserved; it has been cloned in numerous mammalian species, included marsupials, and there are analogues of this gene in birds, reptiles, amphibians, and fish; the latter posseses two PrP genes, PrP1 and PrP2 [5]. Upon processing that removes 22 amino acids from the N-terminus and 23 amino acids from the C-terminus, the mature human PrP^{C} is a 209 amino acid long protein containing two potential sites for N-linked glycosylation (Asp 181 and Asp 197) and a C-terminal glycophosphatidylinositol (GPI) anchor that tethers the protein to the outer surface of the plasma membrane. The central event in the pathogenesis of TSE diseases is the conversion of PrP^{C} to PrP^{Sc}. In contrast to a largely α-helical and monomeric PrP^{C} that is readily degraded by proteolytic enzymes, PrP^{Sc} is a protein aggregate that is rich in β-sheet structure and possesses a characteristic proteinase-resistant core region. In 1982, Prusiner proposed that PrP^{Sc} itself represents the infectious the infectious agent causing TSE diseases [6]. Once revolutionary and highly controversial, this 'protein-only' model is now supported by wealth of experimental data, [7-9] most notably the recent success in generating infectious prions in vitro from highly purified prion protein [10]. Thus, the notion that misfolded proteins can be "infectious" has emerged as a new paradigm in molecular biology and medicine.

One of the characteristic features of human PrP^{C} is the methionine/valine (Met/Val) polymorphism at codon 129. Furthermore, two types of major PK-resistant PrP^{Sc} fragments are observed in sporadic CJD cases (Figure 8). One of them is characterized by electrophoretic mobility (for an unglycosylated form) of 21 KDa (type 1) and another one of 19 kDa (type 2), suggesting different PrP^{Sc} conformations.

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The combination of the status of codon 129 Met/Val genotypes with these two distinct PrP^{Sc} conformers provides a basis for phenotypic classification (or 'strain' variability) of sporadic CJD diseases [11]. The combinantion of codon 129 Met/Val with specific mutations in *PRNP* is also the major determinant of strain variability in familial prion diseases. In this article, we briefly review different forms of human prion disorders associated with these individual mutations.

Silent Polymorphisms

There are several silent polymorphisms within OFR (open frame of reading, a gene sequence encoding for a protein) of the *PRNP* gene

Pro68Pro (CCT=>CCC)

Ala117Ala (GCA=>GCG)

Gly124Gly (GGC=>GGG)

Val161Val (GTG => GTA)

His177His (CAC =>CAT)

Glu212Glu (CAG=>CAA)

Arg228Arg (AGA =>AGG)

Ser230Ser (TCG =>TCA)

Familial CJD

The codon 178^{Asp} 129^{Val} mutation

Goldfarb et al. [12] found a mutation in codon 178 within the *PRNP* gene in a large Finnish family with CJD. A G to A mutation at codon 178 was found resulting in an Asn to Asp substitution. This mutation was found in several families included the famous Backer family in which hereditary CJD was first described. It manifests clinically as otherwise typical CJD, but onset is earlier and there are no typical periodic EEG and myoclonic jerks.

Fatal Familial Insomnia

The codon 178^{Asp} 129^{Val} mutation

The same mutation but coupled with 129^{Met} is linked to Fatal Familia Insomnia (FFI) [13]. The phenotype consists of sleep disorders, nocturnal hallucinations, behavioral disturbances and autonomic dysfunctions. Neuropathologically, changes are confined to the thalamus and aggregates of PrP^{Sc} may be focal and very limited.

The codon 180^{Iso} 129^{Met} mutation

The age of onset varied between 66 and 85 years while duration between 1 and 2 years [14-17]. Phenotypically it is a typical CJD except for the lack of periodic EEG in the majority of cases. Pathological laughing and crying was suggested as a characteristic symptom. MRI demonstrated signal hyperintensity in cortical and subcortical location.

The codon 183^{Val} 129^{Met} mutation

This mutation is characterized by Parkinsonism and dementia similar to the frontotemporal dementias. Neuropathology included spongiform change [18,19].

The codon $188^{Arg\ (Ala\ or\ Lys)}$ $129^{Val\ or\ Met}$ mutation

Phenotypically, the 188^{Lys} mutation manifested in a 59-year-old patient as a rapidly progressive dementia, and dysphasia. The case of 188^{Arg} was a 55-year-old man with behavioral disturbances, dementia, some leg dysmetria and sensory changes; inconclusive 14-3-3 in the CSF and MRI scan revealed hyperintensity in the cortical ribbon, putamen and caudate. Neuropathology was typical for CJD with some balloon neurons. The EEG demonstrated either periodic pattern or diffuse slowing. The case 188^{Ala} was an 82-year-old woman with typical periodic EEG and positive 14-3-3 in the CSF [20,21].

The codon $193^{Iso}129^{Val}$ mutation

This was a 70-year-old case with gait disturbances, behavioral problems and dementia, Babinski sign and myoclonus. There was typical periodic EEGand CSF was positive for the presence of the 14-3-3-protein [22].

The codon 196^{Lys} 129^{Met} mutation

This mutation is characterized by rapidly progressive dementia with no periodic EEG. The age of onset is between 63 and 77 years; duration less than 1 year [23].

The Association of CJD Cases of Eastern European Origin and in Sephardic Jews: Mutation; The Codon 200^{Lys} 129^{Met} Mutation

The codon 200 mutation is associated with a Glu to Lys substitution. Several healthy individuals from affected families at the risk for CJD were tested positive for the presence of the 200 codon mutations. The latter finding is of utmost interest, suggesting that the mutation itself is not sufficient for the development of the disease (or that penetration of this mutation-linked disease is not complete).

The phenomenon of CJD clustering among Libyan Jews have been known for several years, but the clinical features of CJD cases of Libyan origin did not differ significantly from those of sCJD cases of different origin. An extensive search for the putative iatrogenic factors responsible for the high frequency of CJD in this population has been published [24]. Particularly, the high proportion of brain consumption (79 to 92% of CJD cases) was found but frequency of this phenomenon did not differ significantly from that encountered among control subjects. It is noteworthy that brains were consumed as stew (m'chuma), patty (m'akod) or slightly (5 minutes) grilled.

The clinical phenotype had been studies for more than 20 years [25-30]. The age of onset varied between 35 and 66 years and the duration between 35 and 66 years. The picture is consistent with otherwise typical sporadic CJD except that occurrence of progressive supranuclear palsy and peripheral neuropathy was described. Fasciculations were noticed. EEG revealed periodic pattern. The haplotype 200^{Lys} 129^{Val} is characterized by a different phenotype [31] which consists of plaque-like PrP deposits and type 2 PrP^{Sc}.

The codon 203^{Iso} 129^{Met} mutation

The disease started at the age 69 and lasted approximately 1 year [32]. Phenotype corresponded to otherwise typical CJD.

The codon $208^{Arg}129^{Met}$ mutation

The age of onset is 69 [11]. Phenotypically this is a typical CJD with myoclonic jerks and periodic EEG.

The codon $208^{His}129^{Val}$ mutation

This was a 61-year-old woman with behavioral disturbances, dementia, rigidity, no myoclonic jerks and progressive supranuclear palsy syndrome [33,34].

The codon 210^{Iso} 129^{Met} mutation

Phenotypically this is a typical CJD; disease started between 49 and 70 years of age and lasted between 3 – 5 months [35-37].

The codon 211^{Iso} 129^{Met} mutation

Phenotypically this is a typical CJD with periodic EEG; disease started between 42 and 81 years of age and lasted between 3 – 32 months [38].

The codon 226^{STOP} 129$^{Met\ Val}$ mutation

One case in a 55-year-old woman with cognitive impairment, acoustic and visual hallucination, myoclonic jerks and eventually akinetic mutism was described [39]. The major finding was a diffuse amyloid PrP^{Sc}-angiopathy (Figure 1) accompanied by synaptic PrP^{Sc} deposits. Focal MAP-tau deposits were present around blood vessels.

The codon 232^{Arg} 129^{Met} mutation

This is an interesting mutation as it is not only linked to two different phenotypes of familial CJD syndromes but also mutation at this codon is linked to the GSS. FCJD with this mutation is either "slow" or "fast" in regard to duration of the disease. The onset is from 50 to 70 years; EEG showed a typical periodic pattern and a test for 14-3-3 is positive [40-43].

Octarepeat Expansions

In the region 51-91 of the PRNP gene there are four perfect octarepeats (R1, R2, R2, R3, R4) of sequence Pro-His-Gly-Gly-Gly-(-Gly)-Trp-Gly-Gln and 1 pseudoreapet in which His is replaced with Gln. The His-Gly-Gly-Gly-Trp peptide is in a β-turn conformation wrapped around a copper iron [44]. This region is not a part of rP27-30 and the mechanisms by which octapeptide expansions lead to CJD or GSS is unknown.

Additional Repeats *[45]*

1 octapeptide (repeat 24 bp insert, 129^{Met}) (R1 R2 R2 R2 R3 R4 or R1 R2 R2 R3g_R3 R4) Age of onset, 58 – 73 years; duration, 4 – 10 months. Typical CJD phenotype with myoclonic jerks and periodic EEG pattern.

2 octapeptides (repeat 48 bp insert) (R1, R2, R2, R3, R2a, R2a, R4)

129^{Met}, age of onset, 58 years; duration, 3 months. Typical CJD phenotype with myoclonic jerks and periodic EEG pattern; 129^{Val}, dementia and ataxia, more like GSS

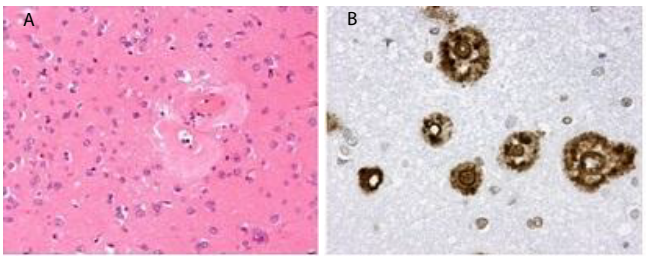

Figure 1: PrP-amyloid angiopathy in a case of the codon 226^{STOP} 129$^{Met\ Val}$ mutation
A: H & E
B: PrP immunohistochemistry. Courtesy, of Dr. C. Jansen, Klinisch Patholoog Stichting Laboratorium Pathologie Oost-Netherlands.

4 octapeptides (repeat 96 bp insert) (R1, R2, R2, R2, R2, R2, R2, R3, R3)

129^{Met}, age of onset, 56 – 65 years; duration, 2 months – 7 years. CJD-like phenotype; 129^{Val}, age of onset, 82 years; duration, 4 months. CJD-like phenotype.

5 octapeptides (repeat 120 bp insert 129^{et}) (R1, R2, R2, R3, R2, R2, R3, R3, R3, R4)

Age of onset, 26 – 61 years; duration, 4 – 19 months. Typical CJD but with long duration of disease, up to 14 years and personality changes observed since early childhood; 129^{Val}, age of onset, 46 years; duration, 4 months.

6 octapeptides (repeat 144 bp insert 129^{Met}) (inserts: R1, R2, R2, R2, R3, R2, R3g, R2, R2, R3, R4 or R1, R2, R3, R2, R2, R3g, R2, R3g, R2, R3, R4 or R1, R2, R2, R2, R2, R2, R2, R2, R2, R3, R4)

Age of onset varies between 22 and 53 years and the disease lasts from a few to 15 years. Clinically, CJD-like phenotype, dementia and focal signs, including the Babinski sign, are the main signs and symptoms. Characteristic are premorbid personality and behavioral changes, noticed even in nearly childhood as aggression, rapid mood changes, antisocial and criminal behavior and hypersexuality. Severe myoclonic jerks are typical. No periodic pattern of EEG was observed. Neuropathologically, linear deposits of PrP^{sc} situated perpendicularly to the cerebellar surface and kuru plaques in a single case were observed. Another case of a GSS phenotype in a 65-year-old woman was recently described [46] (Figure 2). The spongiform change was widespread and kuru-like and multicentric plaques were seen in the cerebellar cortex. The sequence of repeats was: **R1, R2, R2, R3, R2, R3g, R2, R2, R2, R3, R4.** The PrP^{Sc} was of 7 kDa species. Still another case was described by Gelpi et al. [47].

7 octapeptides (repeat 168 bp insert 129^{Met}) (R1, R2, R2, R2',R3, R2, R3, R3, R2, R3, R2", R3, R4). Age of onset, 25 – 35 years; duration, 7 – 16 months. This family presented a CJD-like phenotype with dementia, myoclonic jerks and extrapyramidal signs and symptoms.

8 octapeptides (repeat 192 bp inserts 129^{Met} or 129^{Val}) (R1, R2, R2, R3, R2, R2, R2, R2, R2, R2, R2, R2q, R4)

Age of onset, 21 – 34 years; duration, 12 months – 7 years. Some families are characterized by heterogeneity of signs and symptoms from CJD-like with periodic EEG to GSS-like disease. Numerous amyloid multicentric plaques. 129^{Val}, numerous multicentric plaques; GSS-like-phenotype.

9 octapeptides (repeat 216 bp insert 129^{et}) (R1, R2, R2, R3, R2, R3, R3g, R2, R2a, R2, R3, R2, R3, R4)

Age of onset, 32 – 55 years; duration, 2 to more than 4 months.

Gerstmann-Sträussler-Scheinker Disease

Gerstmann-Sträussler-Scheinker Disease (GSS) is a slowly progressive hereditary autosomal dominant neurodegenerative disease. It is the first human prion disease in which a mutation was discovered, establishing a solid link between the prion protein and these neurodegenerative disorders. GSS diseases are very rare, with the prevalence in the range of 1–10 per million [45].

According to Budka et al. [48] GSS is defined as a neurodegenerative disease "*in family with dominantly inherited progressive ataxia and/or dementia: encephalo(myelo)pathy with multicentric PrP plaques*".

The original Austrian "H" family had been known in Vienna since

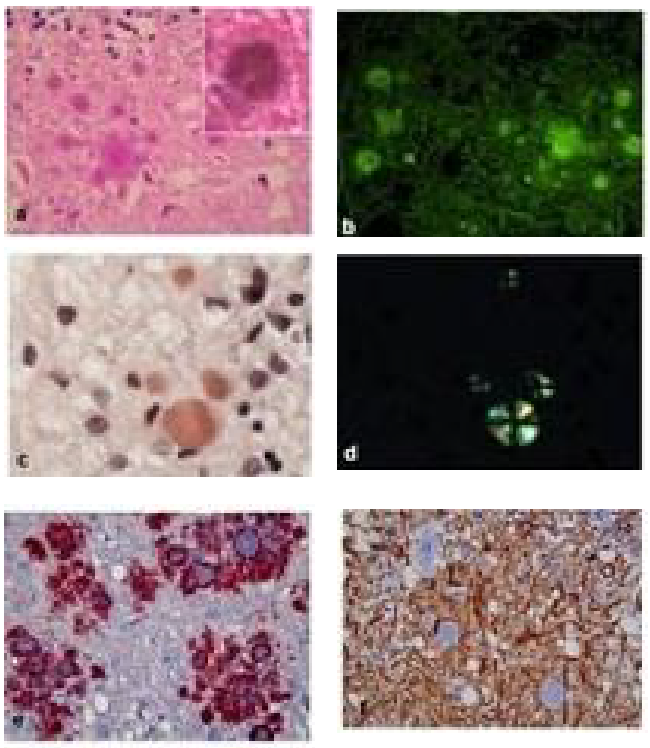

Figure 2: Amyloid plaques from a case of six octarepeats insertions [46]. Courtesy of Dr. Anne Vital, Victor Segalen-Bordeaux 2 University, Institute of Neurodegenerative Diseases, Bordeaux, France
A: H & E
B: Thioflavine S
C: Congo red
D: birefringence
E: anti PrP
F: GFAP staining

the XXth century and was reported by Dimitz in 1913, [49] then by Gerstmann in 1928 [50] and again by Gerstmann et al. in 1936 [51]. In the 1936 original paper, the first name of Scheinker, Isaak, was replaced by the initial "I". In Austria merely 3 years before Nazi takeover, it was risky to admit a Jewish extraction. Later on, Scheinker emigrated to the U.S. where he became a well known neuropathologist, who published, among other works, "*Neuropathology In Its Clinicopathologic Aspects*" [52].

Subsequent members of the same family were described by von Braunmühl [53] and Franz Seitelberger [54,55] Seitelberger, four years before the discovery of the transmissible nature of kuru by Gajdusek et al. [56] stressed the close neuropathological similarity in a form of amyloid plaques of kuru and GSS and in a sense "preconceived" the transmissible nature of GSS [57]. The history of original GSS "H" family from Vienna is interesting. This family originated from a small rural town in the lower Austria and had been diagnosed by local doctors as suffering from hereditary neurosyphilis. As this diagnosis stigmatized them, they decided to hide from doctors. In 1990, Professor Herbert Budka consulted on a female case suspected of CJD whose father died with a diagnosis of "Friedreich ataxia". The maiden name of this case "H" was the name of the GSS family [58,59]. This discovery enabled modern studies of those fascinating kindred.

Several GSS cases belonging to a few then well-known families were described as transmissible to non-human primates [57]. The Fujisaki strain of GSS (codon 102 mutation) first isolated by Tateishi et al. [60] was passaged to mice, rats, guinea pigs and Squirrel monkeys. Another case with the same mutation [61] was passaged to Spider monkeys. This passage was later confirmed by transmission to Marmosets [62]. To date, only inocula derived from 5 brains with 102^{Leu} transmitted [63].

The codon 102^{Leu} 129^{Met} mutation

At codon 102, a mutation leading to a substitution of Pro (CCG) by Leu (CTG) was found [64]. This mutation was subsequently found in several families from Japan [65-71], Germany [72,73] – in the well described Sch. family [74-77], Israel [78], Hungary [79], Poland [80], UK [81,82], Italy [83-85] and in the original Viennese "H" family [86]. Japanese cases are interesting, as before the era of molecular biology they were regarded as CJD cases with abundant plaques [87] while in reality these were GSS cores.

The original family from which 4 cases were described by Seitelberger [55] numbered then 81 members; currently the genealogical tree was expanded to 221 member including 20 definitive GSS cases [58]; no update exists, Hainfellner – personal communication]. As in other GSS families linked to the 102 codon mutation, the disease manifests as slowly progressive cerebellar ataxia with dementia appearing late in the course of disease. The last case of GSS from this family (children of her were tested for a mutation and proved negative for the codon 102 mutation) exhibited, however, features of otherwise typical CJD – i.e. early symptoms of dementia and a characteristic periodic EEG.

For some GSS families with the 102 codon mutation, a typical feature is heterogeneity of neurological signs and symptoms. The classical ataxic type starts in second to sixth decade and the duration of the disease ranges from a few months to a few years. Ataxia, dysartria, and disturbances of saccadic eye movements, pyramidal and extrapyramidal signs and symptoms and cognitive changes leading to frank dementia have been listed among typical features. The latter leads, in a terminal phase of the illness, to the stage of akinetic mutism. Sympathetic hyperactivity and parasympathetic hypoactivity, similar to those encountered in FFI were reported [88]. Hyperthermia, tachycardia and hyperhidrosis were observed. In a proportion of cases, a CJD-like disease type with myoclonic jerks and periodic EEG pattern is observed. In those cases, the accelerated course leading to death in 5–9 months, also typical for sCJD, is seen.

A separate issue is the status of the codon 129 in combination with a mutated codon 102. In the vast majority of GSS cases with the codon 102 mutation, 129^{Met} is observed on a mutated allele [64,73,89-91]. Cases coupled with 129^{Val} are rare. A case described by Young et al. [92] was a 33-year-old male, clinically significantly different from those of 129^{Met}, by the presence of seizures as a initial sign, lower limb paraesthesias and bilateral deafness but not dementia.

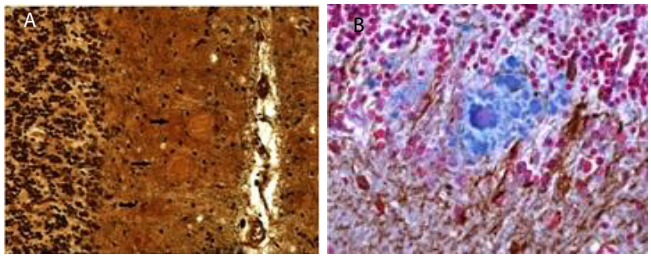

Figure 3: Neuropathology of amyloid plaques from a case GSS 102^{Leu} from original Austrian family.
A: Bielschowsky silver impregnation; amyloid plaques marked with arrows
B: Alcian blue staining

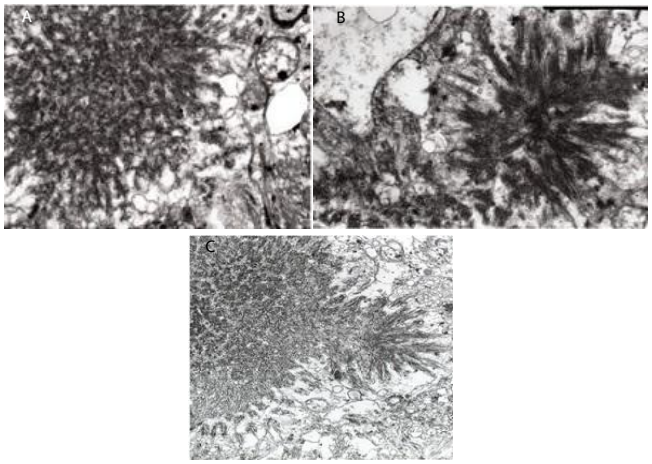

Figure 4: Electron microscopy of GSS plaques
A: unicentric plaque, original magnification, x 8300
B: unicentric plaque, original magnification, x 10 000
C: a budding of a small plaque from a large core, original magnification, x 8300.

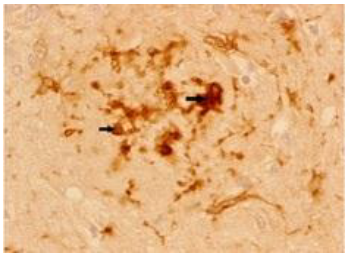

Figure 5: Microglial cells (arrows) within a perimeter of amyloid plaque. Anti-ferritin abs staining.

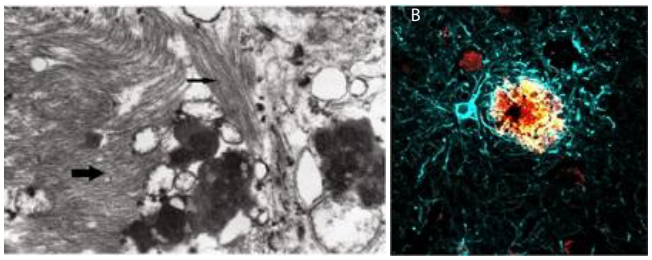

Figure 6: A: Electron microscopic view of a reactive astrocyte around the amyloid plaque, glial filaments are marked with arrows; original magnification, x 10 000
B: confocal laser microscopy view of amyloid plaque (yellow-reddish) surrounded by GFAP-immunopositive astrocytes (blue), courtesy of Dr. Beata Sikorska, Lodz, Poland.

Neuropathology of GSS is characterized by the widespread presence of amyloid plaques in the cerebellum, cortex and subcortical structures (Figure 3). Plaques are either "kuru" plaques – with one core with "spikes", unicentric plaques without "spikes" or multicentric with several overlapping cores (Figure 4). Microglial cells (Figure 5) and reactive astrocytes (Figure 6) are observed within amyloid plaques [93,94]. Dystrophic neuritis is abundant (Figure 7). In cases with CJD-like phenotype, a typical spongiform change are seen

Amyloid plaques are labeled with antibodies raised against PrP 90-102 and, in much smaller proportion, with antibodies raised against peptide PrP 58-71 [95]. Plaque cores were also strongly stained with Abs raised against residues 95-108, 127-147 and 151-165. Antibodies rose against PrP residues 23-40 (N-terminus) and 220-231 (C-terminus) stained peripheries of plaques as ring-shaped structures. The latter findings indicate that both truncated peptides and full-length PrP may form amyloid fibrils but the truncated fibrils predominated. Another analysis revealed bands of 30, 25 and 20 kDa and a single band of 8 kDa, originated exclusively from mutated allele [96]. In addition, PrP^{Sc} sensitive for proteinase K (PK) treatment was found and this species ($sPrP^{Sc}$; "s" from "sensitive") was more abundant that the PK resistant band. Also C-terminal PrP fragments of 16-17 kDa and 12-14 kDa were detected; thus the composition of PrP^{Sc} is more heterogeneous than previously thought.

Recently a novel method to detect PrP^{Sc} (real-time QUIC [quaking-induced conversion] assay) [97] allow to detected PrP^{Sc} in the CSF of 70% [76.5–100%] of GSS cases [98].

The codon 105^{Leu} 129^{Val} mutation

This mutation was found in 5 GSS families, all from Japan [99-106]. The disease manifests as spastic paraparesis with brisk tendom reflexes and the presence of Babinski sign; in terminal stages, patients become teraplegic, demented, with tremor and limb rigidity. Disease starts around 40–50 year of age and the course is long, 6–12 years. PrP^{Sc} deposits are encountered mainly in the cerebral cortex and less frequently in striatum. The cerebellum is affected only minimally. In two cases, sparse tau-immunoreactive Neuro Fibrillary Tangles (NFT) composed of paired helical filaments was also observed.

The codon 105^{Ser} 129^{Val} mutation

This new mutation in the same codon 105 was described in a 30-year-old patient with a phenotype reminiscent of frontotemporal dementia [107].

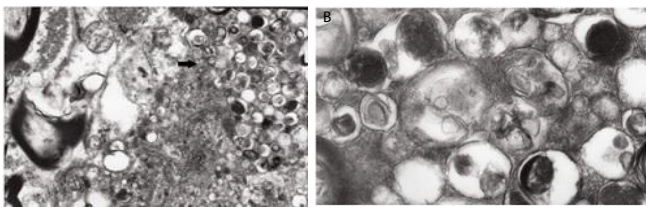

Figure 7: Dystrophic neuritis.
A: a large dystrophic neurite filled with plethora of different subcellular organelles; original magnification, x 8300
B: high power view of the ultrastructure of different subcellular organelles filling a dystrophic neuritis; original magnification, x 33 000.

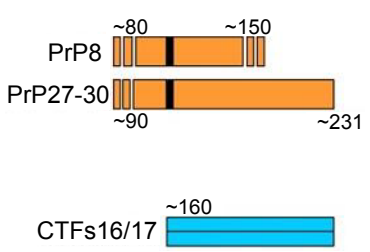

Figure 8: PK-resistant forms of PrP. Those derived from mutant alleles are depicted in orange, those from a wild allele are depicted in blue.Courtesy of Prof. Salvatore Monaco, M.D. Department of Neurosciences, University of Verona, Verona, Italy.

The codon 117^{Val} 129^{Val} mutation

This mutation was discovered in families characterized by dementia but not typical for GSS cerebellar ataxia. Hence, the term "telencephalic type" of GSS was coined [89,108-116] even though the clinical picture is also highly heterogeneous. In an Alsatian family, a generation effect was observed; while in earlier generations only "pure" dementia was observed, in more recent ones a more complex pattern of signs and symptoms was noticed. Amyloid plaques were reactive with antibodies raised against the central region of PrP while antibodies to the C- and N-termini of the molecule stained the peripheries of plaques [117]. The amount of PrP^{Sc} on Western blot was reported to be negligible [118]. However, a 7 kDa PrP^{Sc} was found by Western blot [117,119,120].

Because codon 117 is confined within the sequence STE (STOP-transfer effector) that controls the formation of both transmembrane (PrP^{Ctm}) and secretory (PrP^{Sec}) forms of PrP, [118] that mutation became an ideal target to test the hypothesis that abundance of PrP^{Ctm} may exert a pathological effect as suggested by overrepresentation of PrP^{Ctm} form in GSS brains. The latter phenomenon suggests that the orientation of PrP^{Sc} in regard to the cellular membrane and not merely its presence of this molecule may be important.

The codon 131^{Val} 129^{Met} mutation

This mutation was found in only in two families [121,122]. Clinically, it was characterized by changes in personality, dementia, apraxia, cerebellar ataxia, extrapyramidal signs and brisk tendom reflexes. The disease started in the 5th decade and lasted for 9 years. MRI demonstrated cerebral and cerebellar atrophies. Numerous PrP-amyloid plaques and diffuse deposits were seen in cerebral cortex, basal ganglia and cerebellum (Figure 10).

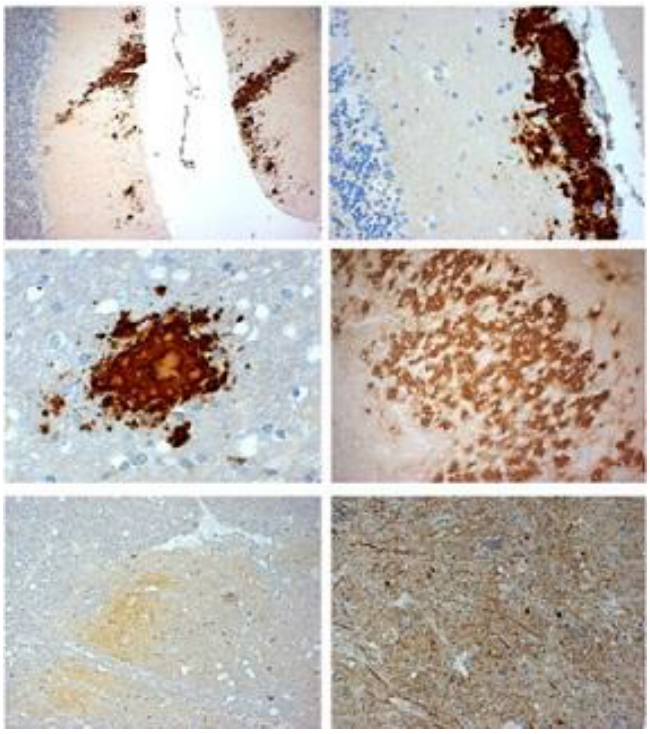

Figure 9: Different forms of amyloid plaques from a case of codon 117^{Val} mutation. Courtesy of Dr. Gabor Geza Kovacs, Neurological Institute, Vienna, Austria.

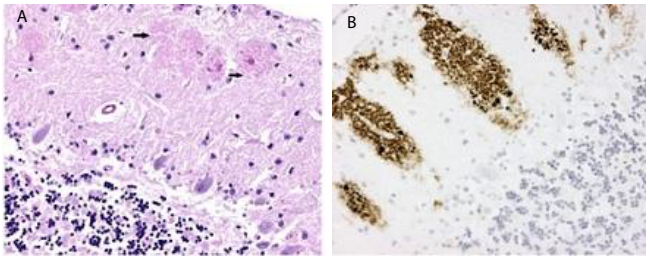

Figure 10: A GSS case with 131^{Val} mutation
A: H & E
B: PrP staining. Courtesy, of Dr. C. Jansen, Klinisch Patholoog Stichting Laboratorium Pathologie Oost-Netherlands.

The codon 145^{Stop} mutation

This mutation was discovered by Kitamoto et al. [123] in a case with spastic paraparesis and progressive severe dementia. Neuropathological examination revealed numerous PrP plaques and PrP deposits in the wall of brain vessels as well as meningeal vessels (PrP-congophilic angiopathy). Tau-immunoreactive NFT was seen in the neocortex.

The codon 187^{ARg} 129^{Val} mutation

This mutation was found in one American family [124]. The age at onset ranged between 33–50 years, and the duration of illness ranged from 8 to 19 years. Clinically, the disease is characterized by dementia, cerebellar ataxia, myoclonic jerks and seizures. Neuropathological examination revealed PrP^{Sc} deposits in cerebral cortex of distinct "curly" appearance and laminar pattern. PrP plaques were absent and spongiform changes were not seen.

The codon 198^{Ser} 129^{Val} mutation

This mutation was discovered in two families from Indiana ("Indiana kindred", IK) [125] and in another unrelated family [126]. Patients harboring mutation of the codon 198 are homozygous or heterozygous in respect to Val at codon 129.

The IK is characterized by pyramidal and cerebellar signs, dementia, dysarthria and progressive difficulties of ambulation.Prominent parkinsonian features – i.e., masked facies, bradykinesia, cogwheel rigidity but no tremors are readily detected [127,128]. Characteristic alterations of saccadic eye movement [129] may be detected before other signs and symptoms appear. Optokinetic nystagmus and sleep disturbances were seen [128,129]. The disease starts between 40 and 70 years of age, and in patients homozygous for 129^{Val}, the beginning is approximately 10 years earlier than in heterozygous cases 129$^{Val\ Met}$ patients. The disease lasts approximately 5 years (from 2 to 12 years), but an accelerated course of 1–2 years is also possible.

PrP-amyloid plaques were seen in the gray matter of neocortex, cerebellum, midbrain, pontine tegmentum and medulla. Plaques were also visible in the striatum, claustrum, the amygdala, the hypothalamus and the thalamus. Some plaques were neuritic. In IK, neurites around plaques contained NFT composed of hyperphosphorylated MAP (microtubulate-associated protein)-tau. Those neurites were also immunoreactive for synaptophysin and βAPP [130]. Spongiform change was occasionally visible around plaques.

Tagliavini et al. [131] showed that plaques are composed of two species of PrP – 7 and 11 kDa spanning PrP residues 81–150 and 58–150, respectively. In contrast, non-fibrillar (pre-amyloid) PrP is immunolabeled with antibodies raised against residues 23-40 and 220-231 [132]. Abs raised against peptide PrP 58-71 stained more plaques

than in GSS 102^{Leu}. In contrast to GSS 102^{Leu}, where Abs raised against PrP residues 95-108 stained plaque cores, in IK, those Abs stained the peripheries of plaques but cores are infrequently stained. Abs rose against PrP residues 23-40 (N-terminus) and 220-231 (C-terminus) stained peripheries of plaques as ring-shaped structures [133].

The codon 202^{Asn} 129^{Val} mutation

The duration of illness of a case with 202^{Asn} was 6 years, the disease started in the 8th decade of life and manifested as dementia with cerebellar signs [134-136]. PrP plaques were seen in both brain and the cerebellum; spongiform change was not present. Numerous NFT were visible in the cerebral cortex. A second GSS family was also indentified [45].

The codon 211^{Asp} 129$^{Val\ Val}$ and the codon 211^{Gln} 129$^{Met\ Met}$ mutation

This mutation was identified in kindred with ataxia and dementia. Neuropathologically the proband was characterized by numerous plaques surrounded by MAP-tau-immunopositive neuritis [137]. Another mutation – 211^{Gln} 129 $^{Met\ Met}$ in the same codon was found in two otherwise typical CJD characterized by spongiform change and no plaques. The PrP Western blot revealed co-occurrence of PrP^{Sc} type 1 and 2A while the GSS case 211^{Asp} was characterized by the presence of otherwise typical for GSS 7 kDa fragment. Biophysical studies suggest that 211^{Asp} PrP has higher propensity to form oligomers that the 211^{Gln} variant; both peptides appear also to differ in the capacity to form salt bridges [137].

The codon 212^{Pro} 129^{Met} mutation

The patient with mutation 212^{Pro} became ill at 60 and the disease lasted for 8 years. Phenotypically, this case demonstrated slurred speech, cerebellar ataxia leading to total incapacitation but not dementia. PrP plaques were visible in both brain and the cerebellum but density of them was the lowest among all GSS families [135]. NMR structure of truncated peptide HuPrP (90-231) revealed different fold from that of the known structures of human PrP^{c} [138]. In particular, α3 helix does not exhibit regular helical conformation in two residues 221^{Glu} and 222^{Ser} which results in breaking of α3 into two smaller helices. There is also different orientation of aromatic residues in β2-α2 loop, resulting in the exposure of the hydrophobic surface of PrP to solvent.

The codon 217^{Arg} 129^{Val} mutation

This mutation was described in 2 patients from a Swedish-American family [110,139,140]. The disease manifests as psychotic manic-depression disturbances, cognitive alterations leading to dementia, ataxia and parkinsonian features. The neuropathological picture is similar to that of IK; numerous PrP plaques and NFT composed of PHF are visible. PrP^{Sc} in plaques coexists with Aβ peptide.

The codon 218^{Asp} 129$^{Val\ Val}$ mutation

This mutation was described in a 61year-old man with non-fluent aphasia, apraxia, agraphia and dysexecutive syndrome, reflex myoclonus and primitive reflexes [141]. Neuropathology consists of uni- and multicentric plaques and robust of MAP-tau-immunoreactive structures, NFT and dystrophic neurites. Western blot for PrP revealed multiple band patterns from 20 kDa to 80 kDa.

The codon 227^{STOP} 129$^{Met\ Val}$ mutation

This mutation was described in a 42-year-old woman with slowly progressive hypokinetic rigid syndrome and cognitive impairment [142]. She also presented tremor in right hand and foot and epileptic seizures. Neuropathologically, she demonstrated numerous multicentric and unicentric plaques, some of them alongside capillaries, numerous MAP-tau-positive tangles in the cerebral cortex and dystrophic neuritis around plaques. PrP^{Sc} was typical for GSS, a 7 kDa species.

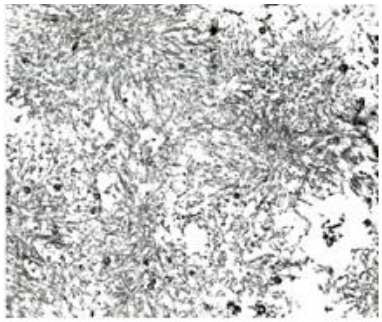

Figure 11: GSS case with 232^{Thr} mutation.
A: Electron microscopic view of merging amyloid plaques, original magnification x 5000.

The codon 232^{Thr} mutation

This mutation was found by Liberski et al. [142,143] in a case diagnosed earlier as olivopontocerebellar degeneration. The disease started in the 5th decade of live and lasted for 6 years. It manifested as spastic paraparesis and dementia. Numerous PrP plaques were visible in the cerebral and cerebellar cortex and subcortical nuclei (Figure 11); in substantia, nigra Lewy bodies were seen occasionally.

Distinct Patterns of PrP^{Sc} in CJD and GSS

Both sporadic and familial forms of CJD are typically characterized by accumulation in the brain of PrP deposits that usually do not stain with amyloid-specific dyes and contain major PK-resistant fragments (for unglycosylated PrP) of 21 and/or 19 kDa, i.e., corresponding to type 1 and type 2 PrP^{Sc}, respectively. These fragments represent C-terminal parts of the prion protein, with major N-termini at residues 82 and 97 for PrP^{Sc} type 1 and type 2, respectively. By contrast, most cases of GSS are characterized by amyloid-like deposits containing smaller fragments of PrP that are truncated both at the N- and C-termini. For example, in GSS with A117V mutation (GSS 117^{Val}) the main component of these amyloid deposits is a 7-KDa peptide corresponding to PrP fragments starting at residues 88/90 and terminating at residues 148/152/153. In GSS with F198S mutation (GSS 198^{Ser}; Indiana kindred, IK), the main components of amyloid plaques are the 11 and 7 KDa PrP fragments corresponding to residues approximately 58-150 and 81-150, respectively [45]. Perhaps the most intriguing situation is presented by GSS cases with P102L mutation (GSS 102^{Leu}), as this mutation appears to be associated with two distinct phenotypes of GSS diseases. While both phenotypes are characterized by diffuse deposits of PrP^{Sc} and PrP amyloid plaques in the brain, only one of them has spongiform degeneration [144]. The latter type is associated with a major PrP^{Sc} fragment of 21-KDa (for the unglycosylated form) and a minor fragment of 8-kDa. The first of these fragments (corresponding to residues ~80-231) is similar to type 1 PrP^{Sc} observed in CJD, whereas the second one (corresponding to residues ~80-150) is similar to those found in other forms of GSS diseases. By contrast, patients without spongiform degeneration show only an 8-kDa PrP^{Sc} fragment [144] (Figure 9).

Interestingly, while sporadic CJD and many cases of familial CJD have been shown to be transmissible in different animal models,

attempts to transmit GSS disease have been successful only for cases with the P102L mutation [63]. Furthermore, recent studies revealed that only the GSS 102^{Leu} disease associated with a 21-kDa PrP^{Sc} could be transmitted to transgenic mice that carry the P102L mutation. By contrast, no transmissibility of clinical symptoms was observed for the GSS 102^{Leu} disease associated with the 8-kDa PrP^{Sc} fragment [145]. Thus, it is possible that only those prion diseases that are associated with longer PrP^{Sc} fragments (containing glycosylation sites and the GPI anchor) are highly transmissible, whereas those associated with N- and C-truncated shorter fragments are more difficult to transmit (or are not transmissible at all).

Biochemical and Biophysical Effects of Pathogenic Mutations

Structurally, the normal form of the prion protein consists of the globular C-terminal domain (residues ~125-228) and a ~100 residue largely unstructured and flexible N-terminal domain (Figure 12). Within the globular domain, there are three α-helices and a short antiparallel β-sheet (2). The distribution of pathogenic mutations is shown in Figure 13, revealing that the vast majority of them congregate within the globular domain. However, a few mutations (P102L, P105L, G114V, A117V, octarepeat expansions) are also found in the flexible N-terminal part. The central question is how these diverse mutations facilitate the conversion of PrP^{C} to the disease-associated PrP^{Sc} isoform, initiating the pathogenic process that eventually leads to neuronal degeneration. One of the earliest hypotheses was that this occurs by mutation-induced decrese in the global thermodynamic stability of the native PrP^{C} isoform. However, experiments revealed that while such destabilization is indeed observed for some pathogenic mutations, many others have a negligible effect on the global thermodynamic stability of PrP. [146,147]. A better correlation was observed in studies probing folding intermediates that may represent direct monomeric precursor in prion protein conversion to the aggregated PrP^{Sc} state, as for the vast majority of PrP variants tested mutations linked to familial prion diseases were found to result in a pronounced increase in the stability (and thus population) of these intermediates [148]. However, even in this case, the effect was not universal for all mutant proteins, suggesting that that there might be a number of different mechanisms by which PrP mutations facilitate the pathogenic process.

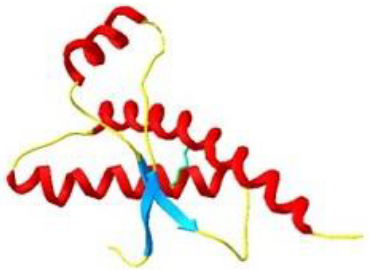

Figure 12: A structureal view of PrP^{c}.

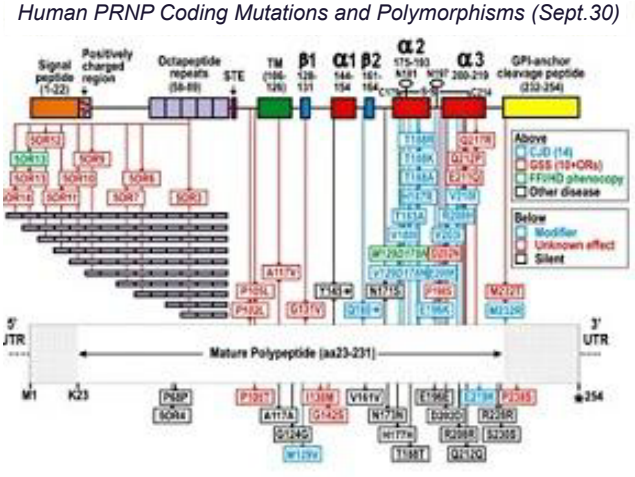

Figure 13: Distribution of all GSS mutations within the *PRNP* gene. Courtesy of Dr. Paul Brown, Bethesda, Md, USA.

The lack of a single universal mechanism that could explain pathogenic effects of all known familial PrP mutations has been further confirmed in numerous structural, biophysical and cellular studies [149]. Overall, it appears that these mutations can produce a host of diverse effects, both at the molecular and cellular level. These include thermodynamic destabilization of the native form of PrP, stabilization of partially structured folding intermediates, altered surface properties of the protein and its interactions with accessory molecules, as well as changes in the metabolic processing and cellular trafficking. There is also no clear correlation between these individual effects and specific phenotypes of prion diseases. It is possible that the phenotypic variability of human prion disorders is largely encoded in distinct structural properties of PrP^{Sc} associated with these different phenotypes. However, direct verification of this general hypothesis is difficult as the detailed structure of PrP^{Sc} remains unknown.

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