Hereditary Human Prion Diseases: an Update

Matthias Schmitz, Kathrin Dittmar, Franc Llorens, Ellen Gelpi, Isidre Ferrer, Walter J. Schulz-Schaeffer, Inga Zerr

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Abstract Prion diseases in humans are neurodegenerative diseases which are caused by an accumulation of abnormal, misfolded cellular prion protein known as scrapie prion protein (PrPSc). Genetic, acquired, or spontaneous (sporadic) forms are known. Pathogenic mutations in the human prion protein gene (PRNP) have been identified in 10–15 % of CJD patients. These mutations may be single point mutations, STOP codon mutations, or insertions or deletions of octapeptide repeats. Some non-coding mutations and new mutations in the PrP gene have been identified without clear evidence for their pathogenic significance. In the present review, we provide an updated overview of PRNP mutations, which have been documented in the literature until now, describe the change in the DNA, the family history, the pathogenicity, and the number of described cases, which has not been published in this complexity before. We also provide a description of each genetic prion disease type, present characteristic histopathological features, and the PrPSc isoform expression pattern of various familial/genetic prion diseases.

Keywords Hereditary human prion diseases · Creutzfeldt-Jakob disease · Fatal familial insomnia · Gerstmann-Sträussler-Scheinker syndrome

Abbreviations
- FFI Fatal familial insomnia
- PRNP Prion protein gene
- PrPSc Scrapie prion protein
- CJD Creutzfeldt-Jakob disease
- gCJD Genetic CJD
- sCJD Sporadic CJD
- OPRI Octa-peptide repeat insertion
- GSS Gerstmann-Sträussler-Scheinker syndrome

Introduction

Transmissible spongiform encephalopathies (TSE) or prion diseases are fatal neurodegenerative disorders, which are characterized by the aggregation and accumulation of misfolded scrapie prion protein (PrPSc) in brain tissue. TSE can occur spontaneously (sporadic), hereditary or acquired, most as iatrogenic cases. Hereditary prion diseases are categorized by certain clinical and pathological features as familial CJD (fCJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), or fatal familial insomnia (FFI). Since more than 50 % of those cases have been reported without a family history, the term “genetic CJD (gCJD)” is now being used more frequently than “fCJD” [1]. Genetic CJD describes a single CJD case, where a mutation in the PrP gene seems to make the conversion into the abnormal form more likely. In some cases, it is difficult to decide whether the mutation is pathogenic or only a polymorphism.
In contrast, in hereditary CJD or fCJD cases, the person has a family history of the disease and a positive test for a genetic mutation associated with CJD.

Since the sensitivity of most diagnostic tests (e.g., 14-3-3, RT-QuIC or MRI) is lower in some hereditary diseases such as FFI [2, 3] than in sporadic CJD (sCJD), a detailed clinical examination and clinical history is extremely important. A confirmed diagnosis of a hereditary prion disease requires the detection of a pathogenic PRNP mutation, a progressive neuropsychiatric disorder, and post mortem confirmation at autopsy [4].

The clinical onset of gCJD/fCJD usually occurs at an earlier age (between 30 and 70 years) compared to sCJD [5] and begins with memory impairment, confusion, myoclonus, and ataxia.

Several PRNP mutations (such as V210I or E200K) are associated with a variable disease onset and a heterogenic penetrance [6]. The penetrance of the disease increased with age, e.g., when mutation carriers survive to age over 80 years, the penetrance is almost 100 % [7]. In contrast, at an age of 70 years, the penetrance is markedly decreased [7].

In sCJD patients, the methionine/valine (M/V) polymorphism at codon 129 of PRNP has a major influence on the susceptibility to and the progression of the disease [8–10]. Similar to sCJD, the clinicopathological phenotype in gCJD/fCJD may also depend on the M/V polymorphism at codon 129 of the mutated allele, e.g., in E200K carriers [11]. In octa-peptide repeat insertion (OPRI) mutation carriers, PRNP codon 129 M/M carriers exhibit an earlier disease onset compared to M/V carriers [5, 12]. However, in most of the genetic cases the influence of the PRNP codon 129 polymorphism on the clinicopathological phenotype has not yet been described well because of the rareness of the cases.

In certain PRNP mutations, e.g., D178N, the codon 129 polymorphism may even determine two completely distinct phenotypes. Traditionally, the 178 mutation in association with methionine at codon 129 has been termed FFI, while a coupling with valine at codon 129 causes different pathology, so that the disease was called fCJD [13]. In addition to the gene polymorphism in PRNP, more than 50 mutations in the open reading frame of PRNP have been described.

In the present review, we provide an updated overview of the reported mutations, describe major differences in the PrPSc expression profile, and present characteristic histopathological features of selected genetic prion diseases.

Types of PRNP Mutations May Cause Different Kind of Prion Diseases

The 253 amino acid PrP is encoded by the second exon of PRNP [14]. All hereditary prion diseases are caused by a wide variety of mutations in the prion protein gene (PRNP), which is located on the short (p) arm of chromosome 20 (20p12), [15, 16]. All of these mutations are autosomal dominant. Among these mutations, point mutations in certain codons, multiple-point mutations, premature STOP codon mutations, or insertion/deletion of octa-peptide repeats in the N-terminal domain of PRNP have been reported [9, 17–19]. However, PRNP mutations also may appear spontaneously with an unknown family history or with an unknown phenotype.

Hereditary CJD Caused by Point or Insert Mutations

Genetic CJD can be caused by a variety of point mutations which are summarized in Table 1 or by insertion mutations in the octa-peptide region of PrP, summarized in Table 2 (Table 1 and 2). The most common mutations in the European population are mutations at codons 178, 200, and 210. Clinically and neuropathologically E200K and V210I resemble sCJD. The average age of onset is between 50 and 70 years of age, and the disease duration is often less than 6 months. The family history of V210I is relatively low (12 %) compared to E200K (49 %) [9].

In the E200K mutation carriers, immunohistochemical detection of PrPSc aggregates usually show indistinguishable pattern from sCJD (MM1) cases (Fig. 1a); some cases show stripe-like deposits of PrPrSc in the molecular layer of the cerebellum (Fig. 1b, c) [127]. Biochemical typing revealed different types of PrPSc which can be distinguished by the molecular weight (type 1 of 21 kDa, type 2 of 19 kDa) of the unglycosylated PrP isoform. V210I and E200K codon 129 MM carriers show a similar composition of the PrPSc isoform pattern, consisting of di-, mono-, and unglycosylated PrP (Fig. 4b). The PrP pattern is comparable to that of sCJD (MM1) patients (Fig. 4b). PrPSc type 1 is typically associated with fCJD E200K and V210I (PRNP codon 129 MM), while PrPSc type 2 is associated with fCJD E200K codon 129 VV (Fig. 4b).

Hereditary CJD Caused by STOP Codon Mutations

Some point mutations integrate a stop codon at different positions within PRNP resulting in the production of abnormal, truncated forms of PrP. STOP codon mutations are very rare in inherited prion diseases and they are accompanied by unusual phenotypes. Examples of STOP mutations are Y145X (tangle pathology), Q160X, Y163X, Y226X, or Q227X [18, 42, 46, 128]. Of these PRNP STOP mutations, Q160X and Q227X cause an Alzheimer disease-like pathology with either amyloid plaques, neurofibrillary tangle lesions, or both [18, 128].
Table 1  Overview of prion disease-associated point mutations

| Codon  | Change in DNA | Familial history | Pathologic | >1 case | Change in amino acid | PRNP codon 129 | Disease       | Reference |
|--------|---------------|------------------|------------|---------|----------------------|----------------|---------------|-----------|
| 39     | ccg → ctg     | n.d.             | n.d.       | n.d.    | Pro → Leu            | n.d.           | FTLD         | [20, 21]  |
| 52     | n.d.          | n.d.             | n.d.       | No      | Gln → Pro            | MV             | Atypical CJD | [22]      |
| 54     | ggt → agt     | No               | No         | Yes     | Gly → Ser            | MM             | n.d.         | [23]      |
| 84     | n.d.          | Yes              | Yes        | Pro → Ser| MV                  | GSS            | [24]         |
| 97     | agt → atn     | n.d.             | n.d.       | Ser → Asn| MM                  | Probable AD   | [25]         |
| 102    | ccg → ctg     | Yes              | Yes        | Pro → Leu| MM                  | GSS            | [26, 27]     |
| 105    | cca → tca     | Yes              | Yes        | Pro → Thr | VV                  | GSS            | [28]         |
| 105    | cca → tca     | n.d.             | n.d.       | Pro → Ser| VV                  | GSS            | [29]         |
| 114    | ggt → gtt     | Yes              | Yes        | Gly → Val| MM, MV              | gCJD           | [30]         |
| 117    | gca → gtt     | Yes              | Yes        | Ala → Val| VV                  | GSS            | [31, 32]     |
| 127    | ggc → gtc     | n.d.             | n.d.       | Gly → Val| MM                  | Protective     | against Kuru | [33–36]  |
| 131    | gga → gta     | Yes              | Yes        | Gly → Val| MM, MV              | GSS            | [37, 38]     |
| 132    | agt → att     | n.d.             | n.d.       | Ser → Ile| MM                  | GSS            | [39]         |
| 133    | gca → gtt     | No               | Yes        | Ala → Val| MM                  | GSS            | [40]         |
| 142    | ggc → agc     | n.d.             | Yes        | Gly → Ser| MM, MV              | n.d.          | [23]         |
| 145    | tat → tag     | Yes              | n.d.       | Tyr → Stop| MM                  | GSS, AD       | [41, 42]     |
| 148    | cgt → cat     | Yes              | Yes        | Arg → His| MM                  | fCJD          | [43]         |
| 160    | caa → taa     | Yes              | Yes        | Gln → Stop| MM, MV              | Dementia      | [44]         |
| 163    | tat → tag     | n.d.             | n.d.       | Tyr → Stop| VV                  | GSS            | [45–47]     |
| 167    | gat → nat     | n.d.             | n.d.       | Asp → Asn| n.d.                | n.d.         | [23]         |
| 167    | gat → gtt     | n.d.             | n.d.       | Asp → Gly| MM                  | n.d.         | [23]         |
| 171    | aac → agc     | n.d.             | No         | Asn → Ser| MM, MV              | Unknown       | [48]         |
| 173    | aac → aag     | n.d.             | n.d.       | Asn → Lys| MV                  | n.d.         | [22]         |
| 176    | gtt → ggg     | Yes              | No         | Val → Gly| VV                  | Unusual GSS   | [49]         |
| 178-129V | gac → aac | Yes             | n.d.       | Asp → Asn| VV                  | fCJD          | [50, 51]     |
| 178-129M | gac → aac | n.d.             | n.d.       | Asp → Asn| MM                  | FFI           | [52]         |
| 180    | gtc → atc     | n.d.             | Yes        | Val → Ile| MM                  | gCJD          | [53, 54]     |
| 183    | aca → acg     | Yes              | Yes        | Thr → Ala| MM                  | fCJD          | [55]         |
| 187    | cac → cgc     | Yes              | Yes        | His → Arg| VV                  | Probable GSS  | [56, 57]     |
| 188    | acg → aag     | n.d.             | n.d.       | Thr → Lys| n.d.                | gCJD          | [44, 58]     |
| 188    | acg → gcc     | Yes              | Yes        | Thr → Ala| MM                  | gCJD          | [59]         |
| 188    | acg → agg     | n.d.             | Yes        | Thr → Arg| VV                  | Criteria for CJD| [19, 60] |
| 193    | acc → att     | n.d.             | n.d.       | Thr → Ile| MM                  | Probable CJD  | [61]         |
| 196    | gag → aag     | Yes              | Yes        | Glu → Lys| MM, MV              | fCJD          | [62]         |
| 196    | gag → gcc     | Yes              | Yes        | Glu → Ala| n.d.                | gCJD          | [63]         |
| 198    | ttc → gtc     | n.d.             | n.d.       | Phe → Val| VV, MM              | Probable AD   | [24]         |
| 198    | ttc → tcc     | Yes              | Yes        | Phe → Ser| MV                  | GSS            | [64, 65]     |
| 200    | gag → aag     | n.d.             | n.d.       | Glu → Lys| MV                  | fCJD          | [66]         |
| 200    | gag → ggg     | n.d.             | Yes        | Glu → Gly| MV                  | fCJD          | [67]         |
| 202    | gac → aac     | n.d.             | n.d.       | Asp → Asn| VV                  | GSS           | [68]         |
| 202    | gac → gcc     | n.d.             | n.d.       | Asp → Gly| VV                  | Slow progressive dementia syndrome | [69] |
| 203    | gtt → att     | n.d.             | Yes        | Val → Ile| MM                  | gCJD          | [62, 70]     |
| 203    | gtt → gtt     | n.d.             | n.d.       | Val → Gly| n.d.                | Probable fCJD | [22]         |
| 208    | cg → cac      | No               | Yes        | Arg → His| MM                  | gCJD          | [71, 72]     |
| 208    | cgc → tgc     | n.d.             | n.d.       | Arg → Cys| MM                  | Probable AD   | [25]         |
Further characteristic phenotypes such as cerebral amyloidosis can be observed in Y145X and Y226X carriers [18, 42], while Y163X is accompanied by chronic diarrhea with dysautonomia [46], suggesting a variable phenotype of certain PRNP mutation which is not always typical for a prion disease.

Insertion Mutations

Human PRNP consists of a nona-peptide (PQGGGTWGQ) followed by a tandem repeat of four copies of an octa-peptide (PHGGGWGQ). These repeats are located between amino acid residues 51 and 91. The normal structure of the five repeats has been designated R1-R2-R2-R3-R4. R1 encodes a nona-peptide, while R2 to R4 encode octa-peptides of the formula P(H/Q)GGG(−/G)WGQ.

By non-coding nucleotide differences, R2, R3, and R4 are each distinguished from R1. Patients with an octa-peptide repeat insertion (OPRI) may have either one or up to 12 additional octa-repeats in PRNP (Table 2). The cause of this extra repeat formation might be an unequal crossover and recombination [17].

The clinical picture of this group of patients (>30 cases) may range from that of classical CJD to that of a GSS-type illness of long duration [129]. In most cases, there is a correlation between the length of the inserts, the age of onset and the duration of the disease. With an increase in the insert numbers from one to seven, the duration of the illness can range from 5 to 120 months [15]. The majority of the patients have a chronic course with aphasia, apraxia, cerebral ataxia, extrapyramidal features, and memory loss [17, 116, 119]. However, patients with one, two, or four extra repeats may have a phenotype similar to sCJD [5]. The clinical pathological features of patients with five, six, seven, eight, and nine extra repeats are reminiscent of Gerstmann-Sträussler-Scheinker syndrome or atypical dementia [93, 130].

In octa-peptide repeat insertion patients, immunohistochemical detection of PrPSc aggregates usually show a patchy or tigroid pattern (Fig. 1d–h). Additionally, they may show coarse and plaque-like PrPSc deposits (Fig. 1g, in case of 4 OPRI) or a tigroid pattern (Fig. 1h, 5 OPRI) in the cerebellar cortex. The PrPSc aggregate pattern indicates a similar pattern comparable to sCJD VV2 patients (Fig. 1i). Most of the OPRI patients express the proteinase K-resistant PrPSc type 2 (Fig. 4b) according to the system described by Parchi et al. [10]. In single cases, PrPSc type 1 may be expressed, as shown for a 4-OPRI codon 129 MM (Fig. 4b).

| Codon | Change in DNA | Familial history | Pathologic | >1 case | Change in amino acid | PRNP codon 129 | Disease | Reference |
|-------|--------------|----------------|------------|---------|---------------------|----------------|---------|-----------|
| 209   | gtg → atg    | n.d.           | n.d.       | No      | Val → Met           | VV             | n.d.    | [23]      |
| 210   | gtt → att    | Yes            | Yes        | Yes     | Val → Ile           | MM             | fCJD    | [73, 74]  |
| 211   | gag → cag    | Yes            | Possible   | Yes     | Glu → Gln           | MM             | fCJD    | [62, 75]  |
| 211   | gag → gac    | n.d.           | n.d.       | n.d.    | Glu → Asp           | VV             | gCJD    | [76]      |
| 212   | cag → cgc    | n.d.           | Yes        | n.d.    | Gln → Pro           | MM, VV         | GSS     | [23]      |
| 215   | atc → gtc    | Yes            | Yes        | Yes     | Ile → Val           | MM             | fCJD    | [77]      |
| 217   | cag → ccg    | Yes            | Yes        | Yes     | Gln → Arg           | VV             | GSS     | [78]      |
| 218   | tac → aac    | Yes            | Yes        | Yes     | Tyr → Asn           | VV             | GSS     | [79]      |
| 219   | gag → aag    | n.d.           | n.d.       | Yes     | Glu → Lys           | MM             | GSS     | [80, 81]  |
| 226   | tac → taa    | No             | Yes        | No      | Tyr → Stop          | VV             | GSS     | [18, 80, 81] |
| 227   | cag → tag    | No             | Yes        | No      | Gln → Stop          | VV             | GSS     | [18]      |
| 232   | atg → agg    | Yes            | Yes        | Yes     | Met → Arg           | MM             | fCJD    | [82–84]  |
| 238   | cca → tca    | Yes            | Yes        | Yes     | Pro → Ser           | MM             | fCJD    | [19]      |

Details about the gene codon, change in DNA sequence, familial history, pathology, number of cases, change in amino acid sequence, type of disease, and corresponding reference are indicated for each PRNP mutation. Lacking information is marked as not-described (n.d.)

FFI-Related Mutations

FFI, the most common genetic prion disease worldwide, typically begins with sleep and vigilance disturbances, cognitive deficits, spatial disorientation, hallucinations, autonomic disturbance, and motoric signs with an onset between 36 and 62 years (average: 56 years). FFI was reported initially as thalamic dementia [131, 132]. The duration of the disease depends on the codon 129 MV polymorphism and is between
6 and 72 months with an average duration of approximately 11 months in MM cases while MV cases exhibit an average disease duration of 23 months [3, 52, 133–135]. However, opposed to the first reported FFI patients, more recent studies indicated that the clinical course of patients with a FFI mutation resembled sCJD without any insomnia symptoms. These observations challenge the widely accepted assumption that codon 129 MM homozygosity is always related to a FFI phenotype [135, 136].

Typically, FFI patients exhibit severe neuronal loss in the anterior ventral and mediodorsal thalamic nuclei and the inferior olivary nucleus associated with prominent astrogliosis and microglial activation (Fig. 2a, b). In the cerebellum, extensive Purkinje cell loss can be observed frequently

| Table 2 | Overview of octa-peptide repeat deletion/insertion (OPRI) mutations |
|---|---|---|---|---|---|---|---|
| Coding change | Insert | Sequence | PRNP codon 129 | Disease | >1 cases | Reference |
| None | No | R1,R2,R3,R4 | All | None | n.d. | [17] |
| 24 bp deletion | −1 | R1,R2,R3,R4 | MM | fCJD-like | Yes | [87] |
| 24 bp insertion | 1 | R1,R2,R3,R4 | MM | fCJD | Yes | [86] |
| 48 bp insertion | 2 | R1,R2,R3,R4 | MM | fCJD | Yes | [86] |
| 72 bp insertion | 3 | R1,R2,R3,R4 | MM | fCJD | Yes | [86] |
| 96 bp insertion | 4 | R1,R2,R3,R4 | MM | fCJD | Yes | [86] |
| 120 bp insertion | 5 | R1,R2,R3,R4 | MM | fCJD | Yes | [86] |
| 144 bp insertion | 6 | R1,R2,R3,R4 | MM | fCJD | Yes | [86] |
| 168 bp insertion | 7 | R1,R2,R3,R4 | MM | fCJD | Yes | [86] |
| Details about the coding change, number of inserts, sequence change, codon 129 genotype, kind of disease, number of cases, and corresponding reference are indicated for each PRNP mutation. Lacking information is marked as not-described (n.d.). |
associated with axonal swelling in granule cell layer (torpedoes) (Fig. 2c).

Spongiform changes of the neuropil may be absent or only focally seen in the parahippocampal region (Fig. 2d). Abnormal PrPSc deposits can be absent (Fig. 2e) or only focally seen in areas with spongiform changes (Fig. 2f).

Biochemical typing of FFI reveals the expression of PrPSc type 2 (MW of unglycosylated PrP = 19 kDa). The amount of PrPSc in FFI is typically very low. Additionally, the resistance of PrPSc to proteinase K (PK) is decreased which makes it difficult to detect the proteinase-resistant fragments by Western blot (Fig. 4c). Protein aggregate filtration techniques may overcome these diagnostic problems [124].

In contrast, carriers of the PRNP D178N mutation, which exhibit PRNP codon 129V at the same allele, are classified as fCJD cases. This patient group shows a more abundant PK-resistant PrPSc banding pattern (Fig. 4a). The PrPSc isoform composition revealed an under-representation of the unglycosylated band at 21 kDa (PrPSc type 1) and an enrichment of PrPSc in certain brain regions, such as the parietal and frontal cortex compared to the occipital cortex, striatum, and cerebellum (Fig. 4a).

**PRNP Mutations Causing GSS**

GSS, originally described by Gerstmann et al. [137], has been associated with many different point mutations (e.g.,
mutations at codons 102, 105, 117, Y145 stop mutation etc. (Table 1) or insertional mutations of octa-peptide repeats (Table 2). The most common cause of GSS is a single base exchange at codon 102 which results in an amino acid residue change from proline to leucine (P102L). The onset of GSS occurs at an age between 40 and 60 years and the percentage of family history is 70% [9]. Clinically, GSS is associated with prominent ataxia. Dementia usually occurs at the late stage of the disease over a course of 1 to 7 years [15].

A characteristic feature of GSS is the appearance of large multicentric PrP-amyloid plaques, stained with hematoxylin-eosin, in the molecular layer of the cerebellum (Fig. 3a, b). Spongiform changes are frequently missing. In some GSS patients, the composite of the PrP plaques show a halo (Fig. 3a, d), but in others not (Fig. 3b, c, e, f).

Moreover, prominent neurofibrillary, tau-positive pathology has been observed in patients exhibiting a PRNP mutation at codon 105, 145, and 217 [42, 138, 139].

In Western blot, GSS patients and carriers of the PRNP P102L mutation typically show an additional proteinase K-resistant protein fragment of 7 to 10 kDa of molecular size. A proteinase K-resistant ladder-like PrPSc banding pattern may also occur in GSS patients (Fig. 4d).

**PRNP Mutations with an Unknown Significance**

Phenotypes of different PRNP mutations may be variable. The majority of PRNP mutations are related to a prion or a prion-like disease. However, certain PRNP mutations have also been described in non-prion disease patients. For example, the octa-repeat deletion around codon 82 with a familiar history is linked to phenotype which is similar to Alzheimer’s disease [140]. Another report described a family with a 288 base pair insertion consisting of 12 octa-peptide repeats which exhibited the clinical behavior changes and neuroimaging features of atypical frontotemporal dementia (FTD) cases [123]. Moreover, a recent report has even identified a PRNP variant, the G127V, which completely prevents prion disease as shown in mice but not yet in humans [35].
Fig. 3  Typical neuropathological features of GSS. a, b GSS plaques can be observed in the molecular layer of the cerebellum detectable by conventional hematoxylin-eosin staining. Spongiform changes are absent. Immunohistochemical anti-prion reactions show abundant multicentric plaques. In some cases, composite plaques show a halo (a, d), but in others not (b, e, f). c, d prion PET blot; prion aggregates in dark brown; e, f conventional anti-prion immunohistochemical staining revealed abundant pathological PrPSc deposits in gray matter (brown color reaction).

Fig. 4 Detection of PK-resistant PrPSc isoform profiles by Western blot in gCJD cases. a Analysis of PrPSc isoforms in different brain regions of an fCJD patient carrying the D178N-129 V mutation. The banding pattern of the D178N-129 V patient revealed an under-representation of the unglycosylated band at 21 kDa (prion type 1). b Western blot analysis (described previously [124, 125] of PrPSc profiles from the frontal cortex of different fCJD patients are classified according to their PrP type. E200K 129 M-, 4-OPRI 129 M-, and V210I 129 M carriers express PrPSc type 1 (unglycosylated PrP form: 21 kDa), while E200K 129 V, 4-OPRI 129 V, and 5-OPRI 129 M carriers exhibit PrPSc type 2 (unglycosylated PrP form: 19 kDa). In c, the PrPSc profile of an FFI patient, and in d, the PrPSc profile of a GSS patient is shown. While PrPSc in the FFI patient is less PK resistant with a low representation of the unglycosylated PrP band, the GSS mutation may cause the expression of a characteristic 7–10 kDa PrPSc fragment. Abbreviations: C control, Occ C occipital cortex, Str striatum, Cereb cerebellum, Par C parietal cortex, Front C frontal cortex, EC entorhinal cortex, Thal thalamus.
Conclusion

To date, more than 50 different mutations in PRNP that may result in diverse clinicopathological phenotypes have been documented. Some genetic cases (GSS) even show a co-pathology of PrPSc and amyloid beta plaques or neurofibrillary tangles. STOP mutations in the PRNP cause quite characteristic banding patterns of PK-resistant PrPSc in brain tissue. Since several PRNP mutations show a disease course resembling classical sCJD and appear to occur spontaneously with no family history and with a variable penetrance, they may remain undiscovered.

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