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Hereditary Human Prion Diseases: an Update

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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 (PrP^{Sc}). 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 PrP^{Sc} isoform expression pattern of various familial/genetic prion diseases.

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Abbreviations

FFI	Fatal familial insomnia
PRNP	Prion protein gene
PrP^{Sc}	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 (PrP^{Sc}) 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.

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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 PrP^{Sc} 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 insertional mutations in the octa-peptide region of PrP, summarized in Table 2 (Tables 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 carriers 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 PrP^{Sc} aggregates usually show indistinguishable pattern from sCJD (MM1) cases (Fig. 1a); some cases show stripe-like deposits of PrP^{Sc} in the molecular layer of the cerebellum (Fig. 1b, c) [127]. Biochemical typing revealed different types of PrP^{Sc} 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 PrP^{Sc} isoform pattern, consisting of di-, mono-, and unglycosylated PrP (Fig. 4b). The PrP pattern is comparable to that of sCJD (MM1) patients (Fig. 4b). PrP^{Sc} type 1 is typically associated with fCJD E200K and V210I (*PRNP* codon 129 MM), while PrP^{Sc} 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.	n.d.	Yes	Yes	Pro → Ser	MV	GSS	[24]
97	agt → aat	n.d.	n.d.	n.d.	Ser → Asn	MM	Probable AD	[25]
102	ccg → ctg	n.d.	Yes	Yes	Pro → Leu	MM	GSS	[26, 27]
105	cca → cta	Yes	Yes	Yes	Pro → Leu	VV	GSS	[28]
105	cca → aca	n.d.	n.d.	No	Pro → Thr	VV	GSS	[29]
105	cca → tca	n.d.	n.d.	n.d.	Pro → Ser	VV	GSS	[30]
114	ggt → gtt	n.d.	Yes	Yes	Gly → Val	MM, MV	gCJD	[31]
117	gca → gtg	Yes	Yes	Yes	Ala → Val	VV	GSS	[32, 33]
127	ggc → gtc	n.d.	n.d.	n.d.	Gly → Val	MM	Protective against Kuru	[34–36]
131	gga → gta	n.d.	Yes	Yes	Gly → Val	MM, MV	GSS	[37, 38]
132	agt → att	n.d.	n.d.	n.d.	Ser → Ile	MM	GSS	[39]
133	gca → gtg	No	n.d.	Yo	Ala → Val	MM	GSS	[40]
142	ggc → agc	n.d.	n.d.	Yes	Gly → Ser	MM, MV	n.d.	[23]
145	tat → tag	n.d.	Yes	n.d.	Tyr → Stop	MM	GSS, AD	[41, 42]
148	cgt → cat	Yes	Yes	Yes	Arg → His	MM	fCJD	[43]
160	caa → taa	Yes	Yes	Yes	Gln → Stop	MM, MV	Dementia	[44]
163	tat → tag	n.d.	n.d.	Yes	Tyr → Stop	VV	GSS	[45–47]
167	gat → aat	n.d.	n.d.	n.d.	Asp → Asn	n.d.	n.d.	[23]
167	gat → ggt	n.d.	n.d.	n.d.	Asp → Gly	MM	n.d.	[23]
171	aac → agc	n.d.	n.d.	No	Asn → Ser	MV, VV	Unknown	[48]
173	aac → aag	n.d.	n.d.	n.d.	Asn → Lys	MV	n.d.	[22]
176	gtg → ggg	n.d.	Yes	No	Val → Gly	VV	Unusual GSS	[49]
178-129 V	gac → aac	Yes	n.d.	Yes	Asp → Asn	VV	fCJD	[50, 51]
178-129 M	gac → aac	n.d.	n.d.	Yes	Asp → Asn	MM	FFI	[52]
180	gtc → atc	n.d.	Yes	Yes	Val → Ile	MM	gCJD	[53, 54]
183	aca → acg	Yes	Yes	Yes	Thr → Ala	MM	fCJD	[55]
187	cac → cgc	Yes	Yes	Yes	His → Arg	VV	Probable GSS	[56, 57]
188	acg → aag	n.d.	Yes	Yes	Thr → Lys	n.d.	gCJD	[44, 58]
188	acg → gcg	n.d.	Yes	Yes	Thr → Ala	MM	gCJD	[59]
188	acg → agg	n.d.	Yes	Yes	Thr → Arg	VV	Criteria for CJD are not fulfilled	[19, 60]
193	acc → att	n.d.	n.d.	No	Thr → Ile	MM	Probable CJD	[61]
196	gag → aag	Yes	Yes	Yes	Glu → Lys	MM, MV	fCJD	[62]
196	gag → gcg	n.d.	Yes	No	Glu → Ala	n.d.	gCJD	[63]
198	ttc → gtc	n.d.	n.d.	No	Phe → Val	VV, MM	Probable AD	[25]
198	ttc → tcc	Yes	Yes	Yes	Phe → Ser	MV	GSS	[64, 65]
200	gag → aag	n.d.	n.d.	Yes	Glu → Lys	MV	fCJD	[66]
200	gag → ggg	n.d.	Yes	No	Glu → Gly	MV	fCJD	[67]
202	gac → aac	n.d.	Yes	n.d.	Asp → Asn	VV	GSS	[68]
202	gac → ggc	n.d.	n.d.	No	Asp → Gly	VV	Slow progressive dementia syndrome	[69]
203	gtt → att	n.d.	Yes	Yes	Val → Ile	MM	gCJD	[62, 70]
203	gtt → ggt	n.d.	n.d.	n.d.	Val → Gly	n.d.	Probable fCJD	[22]
208	cgc → cac	No	Yes	Yes	Arg → His	MM	gCJD	[71, 72]
208	cgc → tgc	n.d.	n.d.	No	Arg → Cys	MM	Probable AD	[25]

Table 1 (continued)

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 → ccg	n.d.	Yes	n.d.	Gln → Pro	MM, VV	GSS	[23]
215	atc → gtc	Yes	Yes	Yes	Ile → Val	MM	fCJD	[77]
217	cag → cgg	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.)

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

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

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,R2,R3,R4	All	None	n.d.	[17]
24 bp deletion	−1	R2 or R2,R3 or R2,R4	MM	None	n.d.	[85]
24 bp insertion	1	R1,R2,R2,R2,R3,R4	n.d.	n.d.	n.d.	[86]
48 bp insertion	2	2R1,R2,R2,R3,R2a,R2a,R4	MM	fCJD-like	Yes	[87]
48 bp insertion	2	R1,R2, R2a,R2,R2a,R2a,R4	VV	n.d.	No	[88]
48 bp insertion	2	R1,R2,R2a,R2,R2a,R2a,R4	MV	Dementia	n.d.	[89]
72 bp insertion	3	R1,R2,R2,R3g,R2,R2,R3,R4	VV	gCJD	n.d.	[90]
72 bp insertion	3	R1,R2,R2,R2a,R2,R2,R3,R4	MM	Still healthy	n.d.	[91]
72 bp insertion	3	R1,R2,R2,R3g,R2,R2,R3,R4	MM	Probable fCJD	n.d.	[92]
96 bp insertion	4	R1,R2,R2,R3g,R2,R3g,R2,R3,R4	MM	gCJD	n.d.	[93]
96 bp insertion	4	R2,R3,R2,R3	MM	n.d.	n.d.	[17]
96 bp insertion	4	R1,R2(6),R3,R4	MM	gCJD	n.d.	[94]
96 bp insertion	4	R1,R2,R2,R3,R2,R2,R2,R3,R4	VV	gCJD	n.d.	[86]
96 bp insertion	4	n.d.	MM	gCJD	n.d.	[12]
96 bp insertion	4	R1,R2,R2,R3,R2,R2,R2,R3,R4	MV	gCJD	n.d.	[95]
96 bp insertion	4	R1, R2,R2,R2,R3,R2,R2, R3,R4	MM	Dementia	n.d.	[96]
120 bp insertion	5	R1,R2(2),R3,R2,R3g,R2(2),R3,R4	n.d.	fCJD	Yes	[17]
120 bp insertion	5	R1,R2(2),R3,R2,R2,R2,R2,R3,R4	MM	fCJD	Yes	[97]
120 bp insertion	5	n.d.	MM	Atypical fCJD	n.d.	[98]
120 bp insertion	5	R1,R2,R2,R3g,R3g,R3g,R2,R2,R3,R4	MV	fCJD	Yes	[99]
120 bp insertion	5	R1,R2,R3,R2,R3,R2,R3g,R2,R3,R4	MM	n.d.	n.d.	[100]
144 bp insertion	6	R1,R2,R2,R2,R3,R2,R3g,R2,R2,R3,R4	MM	n.d.	Yes	[101]
144 bp insertion	6	n.d.	n.d.	gCJD	n.d.	[102]
144 bp insertion	6	R1,R2(3),R3,R2,R3g,R2(2),R3,R4	n.d.	n.d.	n.d.	[103]
144 bp insertion	6	R1,R2(2),R3g,R2(2),R3g,R2(2),R3,R4	MM	fCJD	Yes	[104]
144 bp insertion	6	R1,R2,R2,R3,R2,R3g,R2,R3g,R2,R3,R4	n.d.	fCJD	Yes	[105]
144 bp insertion	6	R1,R2,R2,R2(6),R3,R4	MV	fCJD	Yes	[106]
144 bp insertion	6	R1,R2,R2,[R3,R2,R3g,R2,R2,R2],R3,R4	MV	GSS	n.d.	[107]
144 bp insertion	6	R1,R2,R2,R3,R2,R3g,R3,R2,R2,R3,R4	n.d.	gCJD	n.d.	[9]
144 bp insertion	6	R1,R2,R2,R3g,R3,R4	n.d.	gCJD	n.d.	[108]
168 bp insertion	7	R1,R2,R2c,R3,R2,R3,R2,R3,R2,R3g,R3,R4	n.d.	gCJD	n.d.	[109]
168 bp insertion	7	R2,R2,R2,R2,R3g,R2,R2	VV	gCJD	n.d.	[38]
168 bp insertion	7	R1,R2,R2,R2,R2,R2,R3g,R2,R3g,R2a,R3,R4	MM	gCJD	n.d.	[110]
168 bp insertion	7	R1,R2,R2,R3,R2,R2,R3g,R2,R2,R2,R3,R4	MM	gCJD	n.d.	[111]
168 bp insertion	7	R1,R2,R2,R3,R2,R2,R3g,R2,R2,R2,R3,R4	MM	GSS	n.d.	[112]
168 bp insertion	7	R1,R2,R2,R3,R2,R2,R2,R3g,R2,R2,R3,R4	n.d.	Dementia	n.d.	[113]
168 bp insertion	7	R1,R2,R2,R3,R2,R3,R2,R2,R2,R2,R3,R4	n.d.	Spongiform encephalopathy	n.d.	[114]
192-bp insertion	8	R1,R2,R2,R3,R2(7),R2a,R4	VV	GSS	Yes	[115]
192 bp insertion	8	not described in detail	VV	GSS	Yes	[116]
192-bp insertion	8	R1,R2,R2,R3,R2,R2,R2,R2a,R2,R2,R2,R3,R4	MM	GSS	Yes	[117]
192 bp insertion	8	R1,R2,R2,R3g,R2,R2,R2,R3g,R3g,R2,R2,R3,R4	n.d.	HD	Yes	[118]
216 bp insertion	9	not described in detail	MM	GSS	n.d.	[119]
216 bp insertion	9	R1,R2,R2,R3,R2R3,R3g,R2,R2a,R2,R3,R2,R3,R4	MM	GSS	n.d.	[120]
216 bp insertion	9	R1,R2,R2,R3,R2,R3g,R2a,R2,R2,R2,R3g,R2,R3,R4	n.d.	Dementia	n.d.	[121]
216 bp insertion	9	R1,R2a,R2(3),R3,R2(6),R3,R4	MM	Sporadic dementia	n.d.	[122]
288 bp insertion	12	R1,R2,R2,R3,R2,R2,R3,R2,R3g,R2,R3g,R2,R2, R3g,R2,R3,R4	n.d.	FTD	n.d.	[123]

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.)

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

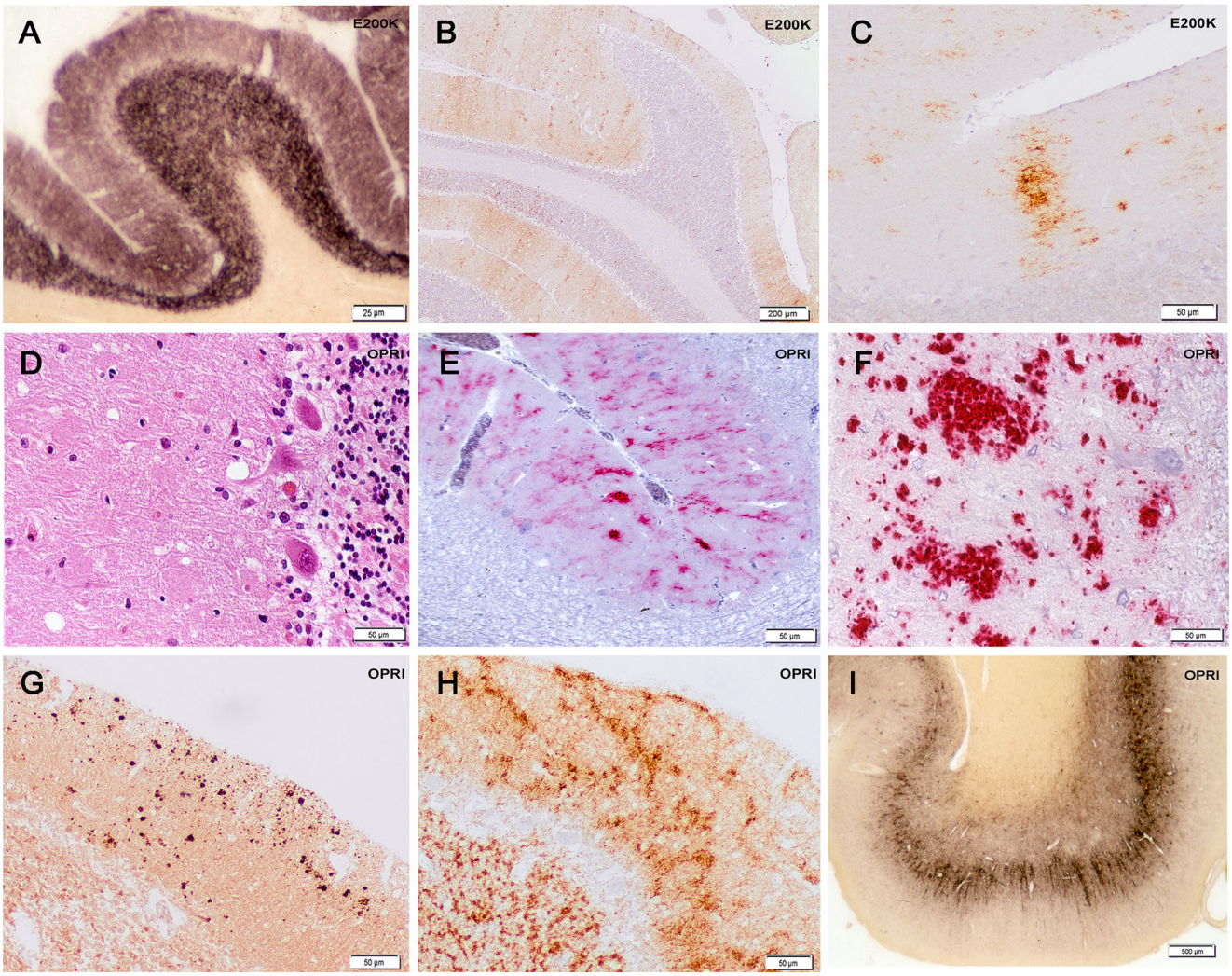

Fig. 1 Histopathological findings in fCJD (E200K. octa-peptide repeat insertion (OPRI)): In E200K patients, immunohistochemical detection of PrP^{Sc} aggregates usually reveal pattern, indistinguishable from sporadic CJD cases (**a**). Some E200K cases may show stripe-like prion deposits in the molecular layer of the cerebellum (**b**, **c**). In octa-peptide repeat insertion patients, immunohistochemical detection of PrP^{Sc} aggregates usually shows a patchy or tigroid pattern (**d**–**h**). Conventional anti-prion immunohistochemistry is depicted either in *brown* (**a**–**c**, **g**–**i**) or in *red color* (**e**, **f**) for visualization, performed according the protocol from [124, 125]. In paraffin-embedded tissue (PET) blots (**a**, **i**; [126]), prion aggregates are stained dark brown. H&E staining in **g** corresponds to immunohistochemistry in **h**. *Magnification bars* are indicated

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 PrP^{Sc} 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 PrP^{Sc} type 2 (MW of unglycosylated PrP = 19 kDa). The amount of PrP^{Sc} in FFI is typically very low. Additionally, the resistance of PrP^{Sc} 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 PrP^{Sc} banding pattern (Fig. 4a). The PrP^{Sc} isoform composition revealed an under-representation of the unglycosylated band at 21 kDa (PrP^{Sc} type 1) and an enrichment of PrP^{Sc} 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.,

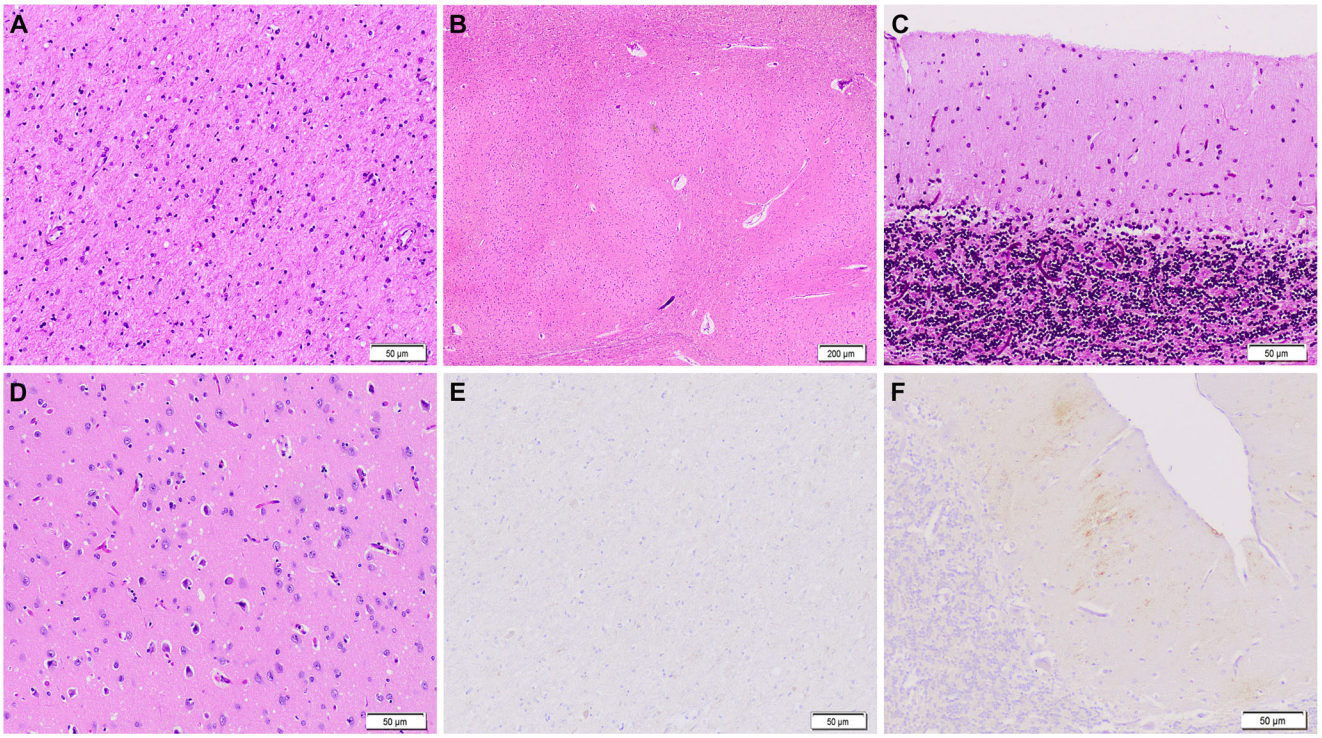

Fig. 2 Representative neuropathological features of FFI. Severe neuronal loss in thalamic nuclei associated with prominent astrogliosis and microglial activation (**a**). Similar changes can also be observed in the inferior olivary nucleus (**b**). In the cerebellum, extensive Purkinje cell loss can be detected (**c**) frequently associated with axonal swelling in the granule cell layer (torpedoes). Spongiform changes in molecular layer are hardly or only focally seen and may be detected in the parahippocampal region (**d**). Similarly, abnormal PrP deposits may be absent (**e**, thalamus) or only focally detectable in areas with spongiform alteration such as the subiculum or cerebellar molecular layer (**f**). **a**–**d** H&E staining; **e**, **f** anti-prion immunohistochemistry [124, 125]

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 fequently 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 PrP^{Sc} 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].

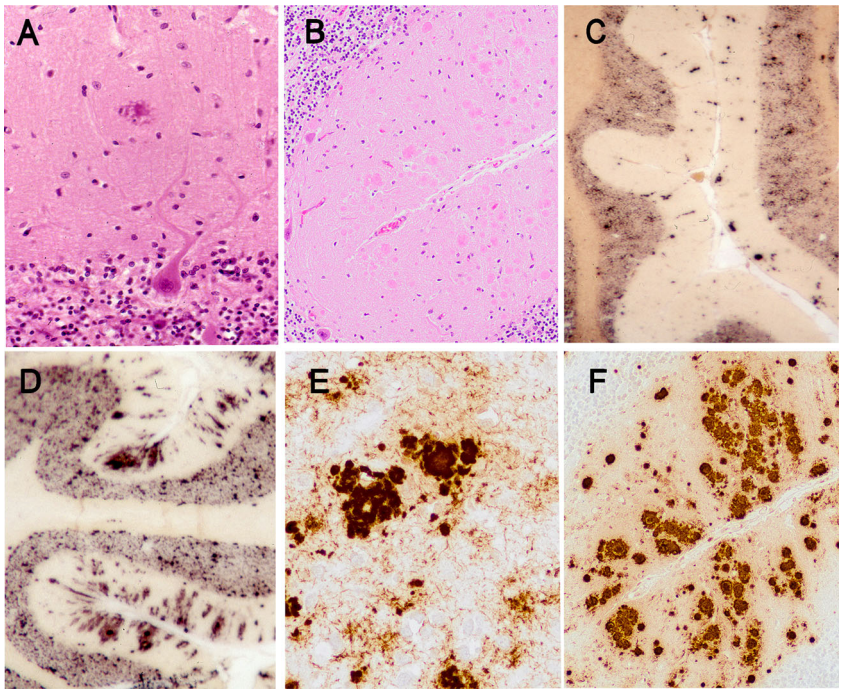

Fig. 3 Typical neuropathological features of GSS. **a**, **b** GSS plaques can be observed in the molecular layer of the cerebellum detectable by conventional hematoxylin-eosin staining. Spongiform changes are absent. Immunohistochemical anti-prion reactions show abundant multicentric plaques. In some cases, composite plaques show a halo (**a**, **d**), but in others not (**b**, **c**, **e**, **f**). **c**, **d** prion PET blot; prion aggregates in *dark brown*; **e**, **f** conventional anti-prion immunohistochemical staining revealed abundant pathological PrP^{Sc} deposits in gray matter (*brown color* reaction)

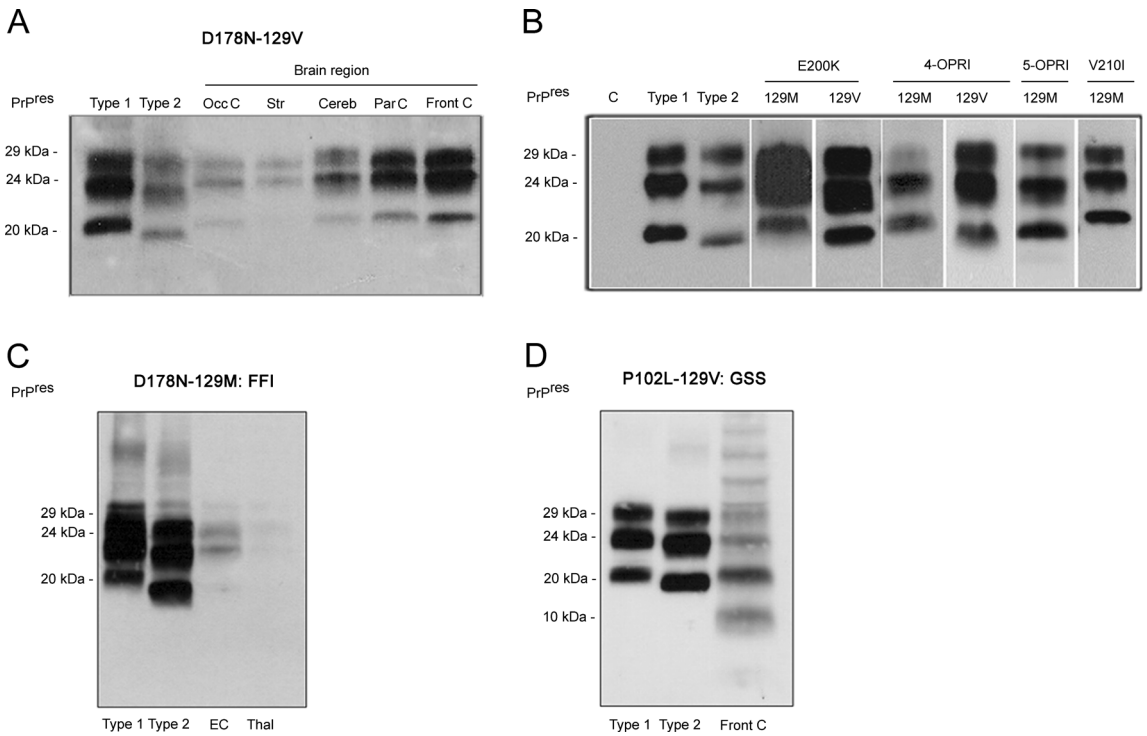

Fig. 4 Detection of PK-resistant PrP^{Sc} isoform profiles by Western blot in gCJD cases. **a** Analysis of PrP^{Sc} isoforms in different brain regions of an fCJD patient carrying the D178N-129 V mutation. The banding pattern of the D178N-129 V patient revealed an under-representation of the unglycosylated band at 21 kDa (prion type 1). **b** Western blot analysis (described previously [124, 125] of PrP^{Sc} 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 PrP^{Sc} type 1 (unglycosylated PrP form: 21 kDa), while E200K 129 V, 4-OPRI 129 V, and 5-OPRI 129 M carriers exhibit PrP^{Sc} type 2 (unglycosylated PrP form: 19 kDa). In **c**, the PrP^{Sc} profile of an FFI patient, and in **d**, the PrP^{Sc} profile of a GSS patient is shown. While PrP^{Sc} 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 PrP^{Sc} 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 PrP^{Sc} and amyloid beta plaques or neurofibrillary tangles. STOP mutations in the *PRNP* cause quite characteristic banding patterns of PK-resistant PrP^{Sc} 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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