Narrative Review Article

Genetic Mutations and Epigenetic Mechanisms Influencing Disease Phenotype in fCJD and GSS Syndrome

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ABSTRACT

This literature review explores the intersection of genotype and phenotype in prion diseases, specifically familial Creutzfeldt–Jakob disease (fCJD) and Gerstmann–Sträussler–Scheinker syndrome (GSS). The relationship between pathogenic PRNP variants and their clinical manifestations, including symptoms, disease severity, and age at onset, remains largely unknown. This review identifies mutations within the PRNP gene associated with both diseases and examines how these genetic differences may influence prion protein misfolding. The presence of mutation-specific phenotypes highlights the sensitivity of prion structure to sequence changes, complicating diagnosis when variants produce overlapping phenotypes. In addition, this review evaluates the role of the PRNP codon 129 polymorphism in disease progression. In certain cases, heterozygosity for methionine and valine at codon 129 is associated with slower neurodegeneration and later disease onset, while homozygosity is associated with faster disease progression and earlier onset. However, these effects appear to depend on the specific pathogenic mutation and genetic background. For example, some patients heterozygous for the D178N variant of fCJD exhibited similar disease duration and severity as homozygous patients, suggesting that additional genetic factors may act as additional disease modifiers. Overall, this synthesis provides a basis for future research into the genetic factors behind prion disease.

Keywords: Biology; Molecular genetics; Prion diseases; PRNP polymorphism; Phenotypic variability in prion diseases

INTRODUCTION

Familial Creutzfeldt–Jakob disease (fCJD) and Gerstmann–Sträussler–Scheinker syndrome (GSS) are prion diseases caused by mutations in the PRNP gene, which encodes prion proteins. These mutations are rare but fatal, since they can cause misfolding of prion proteins from their normal forms, PrP^{C}, to disease-associated forms, PrP^{Sc} (1). Clinical manifestations include memory loss, motor dysfunction, and loss of coordination. These clinical features may overlap with Alzheimer's disease (1).

The cellular prion protein PrP^{C} exists in soluble and membrane-anchored forms and contains a glycosylphosphatidylinositol anchor (1). The C-terminal domain, which contains the anchor, folds into a tertiary structure of three α-helices and two antiparallel β-sheets, with a disulfide bridge between cysteine residues 179 and 214 (2). Two N-glycan sugar chains are attached to amino acids 181 and 197 and contribute to protein stability and cell signaling (2). The functions of PrP^{C} proteins are still being studied. They are believed to play

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Accepted August 13, 2026
https://doi.org/10.70251/HYJR2348.4410691076

a role in sleep regulation through calcium and potassium channel activity, stabilizing neuronal excitability through modulation of ion channels and glutamate receptors, neuroprotection by reducing ischemia-inducing lesions and preventing aggregation of Aβ oligomers, and the maintenance of peripheral myelin through signaling to Schwann cells (3).

Disease-causing prion proteins adopt the PrP^{Sc} form. This isoform is a solenoid composed of four stacked β-sheet layers spaced approximately 4.8 Å apart (4). The C-terminal is located at the core of the fibril from which the N-terminal domains project outward. Since PrP^{Sc} proteins are extremely compact, N-terminal residues are susceptible to proteolytic digestion, leaving the infectious core of the protein relatively unharmed (4). In addition, these proteins are often resistant to heat, radiation, and sterilization. In this manner, the structure of PrP^{Sc} proteins facilitates their rapid propagation and aggregation by resisting degradation (4).

The mechanisms that trigger the conversion of prion proteins from normal PrP^{C} to disease-associated PrP^{Sc} forms are largely unknown. Prion diseases cause neuronal damage as PrP^{Sc} propagates: PrP^{Sc} attaches to PrP^{C} and induces a conformational change from α-helices to β-sheets (5). This misfolded shape acts as a template, converting more PrP^{C} forms into the abnormal shape. As PrP^{Sc} accumulates, it triggers a cascading chain reaction of protein misfolding, resulting in the formation of insoluble clumps of amyloid fibrils (5). This buildup causes neurons to deteriorate and produces spongiform deformation in the brain tissue (5).

The two major prion diseases that this review evaluates are Creutzfeldt–Jakob disease (CJD) and Gerstmann–Sträussler–Scheinker syndrome (GSS).

While there are four subtypes of CJD, the two most prominent subtypes are sporadic (sCJD) and familial (fCJD). sCJD is characterized by the seemingly spontaneous misfolding of prion proteins (Table 1). fCJD results from an inherited pathogenic variant in the PRNP gene (Table 1).

Definitive diagnosis of CJD is achieved through direct examination of brain tissue obtained from a brain biopsy or postmortem autopsy (11). Neuropathological confirmation can be established through positive findings from one of three recognized methods (11, 12). The first method used for diagnosis is immunohistochemistry, in which brain tissue is stained using an edited 3F4 antibody that specifically recognizes PrP^{Sc} protein forms (13). Detection sensitivity may increase with disease progression as the PrP^{Sc} accumulation becomes more widespread (13). The second method is a Western blot using 3F4 antibodies to detect PrP^{Sc} cleaved at different sites (12, 13). The final method is the detection of scrapie-associated fibrils (SAFs) through visualization with electron microscopy (12). SAFs have a rod shape with β-sheet–rich secondary structure similar to that of PrP^{Sc} proteins (14, 15). The presence of SAFs is considered a definitive diagnostic feature of CJD since they are not frequently observed in healthy individuals or patients with other common neurodegenerative diseases, indicating that SAFs may be either a pathological response to or a supporting agent in the development of CJD (16).

Table 1. *Comparison of reported clinical characteristics of sCJD and fCJD derived from published studies. Values represent the study populations cited and may vary across cohorts and PRNP mutations.*

	sCJD	fCJD
Proportion of CJD Cases	Approximately 85-90% of reported CJD cases (6)	Approximately 5-15% of reported CJD cases (6)
Typical Age at Symptom Onset*	~62 years (7)	~46 years (reported for the studied familial cohort) (8)
Reported Disease Duration†	Approximately 8 months (8)	Approximately 22 months (reported for the studied familial cohort) (8)
Common Clinical Features	Rapidly progressive dementia, myoclonus, cerebellar dysfunction, visual disturbances, gait imbalance, and cognitive decline (9)	Dementia, cerebellar ataxia, myoclonus, autonomic dysfunction, insomnia, and progressive motor impairment (9, 10)

** Age at symptom onset refers to values reported in the cited studies and may differ across patient cohorts and PRNP mutations.*
† Disease duration refers to survival after symptom onset (or diagnosis when explicitly reported by the source). Disease duration varies across patient cohorts and PRNP mutations.

A probable diagnosis of CJD can be established when both criteria are met. The first method of diagnosis is real-time quaking-induced conversion (17). This test detects misfolded prion protein in patient samples such as cerebrospinal fluid. Recombinant PrP substrate is added to patient samples, and if PrP^{Sc} is present, it induces a chain reaction that converts the normal protein into more misfolded protein. Thioflavin T dye binds to the aggregates and fluoresces, confirming the presence of PrP^{Sc} (17). The second criterion is twofold: the patient must demonstrate certain neurological symptoms and a positive result on at least one of three tests (18). The neurological symptoms must consist of rapidly progressing dementia and at least two of the following: myoclonus (involuntary muscle jerks), visual or cerebellar signs such as vision loss or hallucinations, pyramidal and extrapyramidal signs (such as rigidity or abnormal movements), and akinetic mutism (loss of voluntary movement and speech) (18). In addition to meeting the minimum requirements for neurological symptoms, patients must demonstrate a positive result on at least one of three tests: abnormal EEG patterns, positive detection of the 14-3-3 CJD-biomarker protein in an assay of cerebrospinal fluid, or high-intensity signaling from an MRI (18).

Gerstmann–Sträussler–Scheinker syndrome (GSS) is a rare, inherited prion disease. While it is similar to fCJD in that it is caused by mutations in the PRNP gene, GSS is neurologically characterized by PrP^{Sc} buildup in different regions of the brain (9, 19, 20) and has different disease phenotypes than those of fCJD (Table 2).

The diagnosis of Gerstmann–Sträussler–Scheinker syndrome relies primarily on clinical evaluation. Laboratory tests or imaging alone cannot definitively confirm GSS (22). Molecular genetic testing can provide a definitive diagnosis (22). Genetic testing may be considered for patients with rapidly developing psychiatric and coordination changes, particularly those with a family history of prion disease (22).

Clinical tests for GSS evaluate the functional and structural brain changes that occur as the disease progresses. An EEG measures electrical activity in the brain and can reveal abnormal patterns associated with neurodegeneration, providing evidence of cortical dysfunction characteristic of prion diseases (22). MRI scans allow visualization of brain tissue, sometimes revealing abnormalities in regions affected by spongiform degeneration (22). While CT scans are less conclusive for detecting GSS, they can rule out other causes of cognitive decline or motor symptoms (22). Single-photon emission computed tomography is a type of imaging technique that evaluates blood flow in the brain by monitoring gamma rays that are emitted by a radioactive chemical tracer in the bloodstream. In GSS, it may reveal areas of reduced blood flow resulting from neuronal degeneration (22).

Although familial Creutzfeldt–Jakob disease (fCJD) and Gerstmann–Sträussler–Scheinker syndrome (GSS) both arise from pathogenic mutations in the PRNP gene, the relationship between specific mutations and disease phenotype remains incompletely understood. Additionally, the mechanisms by which different

Table 2. *Comparison of reported clinical characteristics of GSS and fCJD derived from published studies. Values represent the study populations cited and may vary across cohorts and PRNP mutations.*

	GSS	**fCJD**
Typical Age at Symptom Onset*	~51.6 years (reported for the studied familial cohort) (19)	~46 years (reported for the studied familial cohort) (8)
Reported Disease Duration†	Approximately 2-10 years (20)	Approximately 22 months (reported for the studied familial cohort) (8)
Common Clinical Features	Cerebellar ataxia, dysarthria, muscle rigidity, visual impairment, hearing loss, nystagmus, and progressive cognitive decline (21)	Dementia, cerebellar ataxia, myoclonus, autonomic dysfunction, insomnia, and progressive motor impairment (9, 10)
Predominant Neuropathological Distribution of PrP^{Sc}	Cerebellum and cerebral cortex (20)	Cerebellum, cerebral cortex, and basal ganglia (9)

* Age at symptom onset refers to values reported in the cited studies and may differ among patient cohorts and PRNP mutations.
† Disease duration refers to survival after symptom onset (or diagnosis when explicitly reported by the source). Disease duration varies across patient cohorts and PRNP mutations.

mutations influence prion protein misfolding and the resulting patterns of neuronal degeneration are not fully understood (2, 5). Although substantial progress has been made in characterizing inherited prion diseases, important questions remain regarding the factors that influence disease onset, clinical presentation, and progression (2, 5). Even within families carrying the same mutation, individuals can develop symptoms at different ages, experience disease varying severity, and have different disease durations (19). This variability makes it difficult to predict how the disease will manifest in a given individual. This review synthesizes current evidence regarding mutation-specific phenotypes and disease modifiers in inherited prion diseases to clarify areas of consensus, highlight unresolved questions, and identify priorities for future research.

MUTATION-SPECIFIC PHENOTYPES IN FCJD

E200K Mutation

A cohort study of 30 patients with fCJD identified the E200K PRNP mutation in all affected individuals (23). The E200K mutation occurs at codon 200 of the PRNP gene, where a single nucleotide substitution replaces the amino acid glutamate with lysine (23). DNA sequencing of 21 family members from three families revealed 16 asymptomatic carriers of the E200K mutation (23).

In the reported cohorts, the most common presenting features included dementia, pyramidal or extrapyramidal dysfunction, myoclonus, cerebellar dysfunction, and akinetic mutism (23). Imaging studies of the CJD patients demonstrated gray matter atrophy and decreased apparent diffusion coefficient values in the basal ganglia, indicating restricted water diffusion associated with tissue damage. MR spectroscopy revealed a trend toward neuronal dysfunction with evidence of reduced N-acetylaspartate, a marker of neuronal integrity. Additionally, hyperintensities in the basal ganglia and thalamus reflected abnormal tissue signals consistent with prion-related degeneration (24).

D178N Mutation

A genetic analysis of a patient confirmed a mutation consistent with the D178N variant of fCJD or familial fatal insomnia (FFI) (25). In the reported patient, the mutation was present in one copy of the gene. The D178N mutation occurs at codon 178 of the PRNP gene, where a single nucleotide substitution replaces the amino acid aspartate with asparagine (25).

In the reported case, the patient presented with distinctive neurological features. The reported clinical features included spastic paraparesis, hyperreflexia, clonus, and impaired balance (25). Neuropathologic examination revealed severe loss of Purkinje cells in the cerebellar cortex, astrogliosis in thalamic nuclei, and synaptic loss in the entorhinal cortex. No spongiform changes were observed in the reported patient (25).

V180I Mutation

Genetic analysis of a patient revealed a mutation consistent with the V180I variant of familial CJD (26). The V180I mutation occurs at codon 180 of the PRNP gene, where a single nucleotide substitution replaces the amino acid valine with isoleucine (26).

In the reported patient, progressive neuropsychiatric and cognitive decline was observed. Clinical features included severe depression, irritability, dementia, and hallucinations (26). A case report of another patient with this variant of CJD reported slight volume loss in the right temporal pole, hippocampus, and amygdala (27). Cortical hyperintensities and swelling were observed in the right frontal-parietal lobes, bilateral temporal lobes with right-sided predominance, right striatum, and parahippocampus. Functional imaging showed decreased blood flow in the right frontal, temporal, and bilateral parietal lobes with this variant (27).

MUTATION-SPECIFIC PHENOTYPES IN GSS

P102L Mutation

A family study using postmortem neuropathological examination and DNA sequencing identified the P102L mutation in two individuals with GSS (19). The reported family members had the mutation present in one copy of the gene. The P102L mutation occurs at codon 102 of the PRNP gene, where a single nucleotide substitution replaces the amino acid proline with leucine (19).

Neuropathological examination of the family members demonstrated distinctive hallmark features of GSS. The brains of the affected individuals exhibited severe spongiform degeneration in the upper three cortical layers of the prefrontal cortex. Other brain regions also demonstrated spongiform deformation across multiple neuronal layers, such as in the striatum and other cortical regions (19). Patients exhibited deposits of PrP^{Sc} proteins along synaptic pathways in parts of the hippocampus, including the stratum radiatum and stratum moleculare, as well as in the Purkinje cells and other layers of the cerebellum (19). These pathological findings are consistent with impaired

neuronal communication and may contribute to the memory loss and motor dysfunction observed in affected individuals. PrP^{Sc} deposits accumulated as plaques in the hippocampus, amygdala, cerebellum, basal ganglia, neocortex, and entorhinal cortex in patients with this variant of GSS (19). The widespread distribution of plaques and spongiform degeneration may contribute to the frontotemporal dementia and severe ataxia observed in affected individuals (19). However, in another affected family member, plaque accumulation was found only in the hippocampus, neocortex, amygdala, and entorhinal cortex. This more restricted pattern of pathology was associated with frontotemporal dementia and the absence of ataxia (19).

G131V Mutation

A case report involving neuropathological examination and DNA sequencing identified the G131V mutation in a patient with GSS (28). The G131V mutation occurs at codon 131 of the PRNP gene, where a single nucleotide substitution replaces glycine with valine. This single base substitution alters the prion protein's structure by substituting a small, flexible glycine residue with a bulkier valine residue, which may destabilize the protein and promote its misfolding (28).

Neurofibrillary tangles were observed in the reported patient's hippocampus and entorhinal cortex—regions critical for memory and spatial navigation (28). These tau-positive tangles indicated abnormal accumulation of hyperphosphorylated tau, possibly triggered by the misfolded prion protein. Amyloid plaques were observed in the cerebellum, Ammon's horn, cerebral cortices, corpus striatum, thalamus, and cerebellar layers (28). The widespread distribution of PrP^{Sc} deposits is thought to contribute to neuronal loss and synaptic dysfunction (28). Clinically, the patient developed worsening cognitive impairment, apraxia, tremors, and loss of visuospatial and motor coordination, consistent with degeneration of both cortical and cerebellar regions (28). In this patient, the absence of spongiform degeneration suggests that disease pathology for the G131V variant may be driven primarily by amyloid plaque deposition and tau accumulation.

F198S Mutation

A study of two affected individuals with the F198S mutation confirmed the presence of this PRNP variant through DNA sequencing. The reported patients had the mutation present in one copy of the gene (29). The F198S mutation occurs at codon 198 of the PRNP gene, where a single nucleotide substitution replaces phenylalanine with serine (29).

Neuropathological examination of the reported patients demonstrated distinct patterns of brain damage and clinical symptoms. In one patient, the cerebellar cortex and dentate nucleus were shrunken, and key brainstem regions, such as the substantia nigra and locus coeruleus, were severely depigmented (29). The inferior olivary nuclei also demonstrated noticeable atrophy. Sections of the cerebral hemispheres revealed mild overall atrophy, loss of neurons, and gliosis, along with reduced myelin in the deep white matter of the frontal, temporal, and parietal lobes (29).

PrP^{Sc} deposits appeared as multicentric plaques and diffuse deposits throughout the cortex, subcortical nuclei, cerebellum, and brainstem, which may be associated with disrupted neuronal signaling (29). A reported patient initially developed cerebellar ataxia and dysarthria, followed by bradykinesia and rigidity (29). Neuropathological findings suggested that amyloid deposition preceded tau pathology, highlighting a stepwise progression. The widespread plaques and neurodegeneration may help explain the combination of motor problems and cognitive decline observed, although differences in size and location of the deposits may account for variability in symptom severity among mutation carriers.

CODON 129 AS A MUTATION-SPECIFIC PHENOTYPIC MODIFIER

Codon 129-Associated Phenotypic Variability in fCJD

All 30 patients in the identified cohort with E200K-associated fCJD were homozygous for methionine at the codon 129 polymorphic site (23). The disease course was characterized by more rapid progression compared with other CJD variants. However, direct comparisons of E200K patients with different codon 129 genotypes cannot be made, making the specific contribution of the 129M/M genotype to the clinical symptoms unknown. Thus, rather than solely determining the clinical course of E200K-associated fCJD, the 129M/M genotype may represent one genetic factor influencing the disease progression observed in this mutation.

The clinical phenotype associated with the D178N mutation is strongly influenced by the codon 129 polymorphism of the PRNP gene. When methionine was encoded at codon 129 on the same allele as the D178N mutation, patients presented with familial fatal insomnia, an entirely different prion disease. However, when valine

was encoded at codon 129 on the mutant allele, patients presented with fCJD (25). This allele-specific interaction represents an important example of how codon 129 modifies the phenotypic expression of a pathogenic PRNP mutation. Among most of the individuals studied, methionine homozygosity at codon 129 (129M/M) was associated with shorter disease duration, whereas heterozygosity (129M/V) was associated with a slower disease course (25). However, this relationship was not consistent amongst all individuals, as the disease progression of one reported heterozygous patient remained relatively rapid (25).

The reported patients with the V180I variation of fCJD presented homozygosity for methionine regarding codon 129 polymorphism (129M/M genotype) (26). The disease had a later onset and a slower progression compared to other CJD variants. However, because direct comparisons between V180I patients with different codon 129 genotypes remain limited, the contribution of the 129M/M genotype to this phenotype remains uncertain. Rather than defining the clinical course of V180I-associated fCJD, the 129M/M genotype may represent one genetic factor that contributes to the characteristic slower progression observed in this mutation.

Codon 129-Associated Phenotypic Variability in GSS

Reported individuals with GSS-associated PRNP mutations have demonstrated variability in their genotype at the codon 129 polymorphic site. In a family study of individuals carrying the P102L mutation, the disease-associated PRNP allele also contained the 129M polymorphism, while the other allele contained 129V, resulting in a 129M/V genotype (19). In contrast, the reported patient with the G131V mutation was homozygous for methionine at codon 129 (129M/M genotype) (28). Among reported individuals with the F198S mutation, one patient demonstrated a 129M/V genotype, whereas another was homozygous for valine at codon 129 (129V/V genotype) (29). These observations indicate that GSS-associated PRNP mutations occur across multiple codon 129 genetic backgrounds, allowing investigation of how this polymorphism may contribute to variation in disease phenotype.

Studied patients with codon 129 heterozygosity (129M/V) carrying the P102L and F198S mutations have demonstrated variable neurological manifestations, including cerebellar ataxia, speech impairment, and progressive cognitive decline, with symptom progression occurring in a stepwise manner in reported cases (19, 29). Conversely, codon 129 homozygosity has been observed in individual patients with severe clinical and neuropathological findings. For example, the reported G131V patient with a 129M/M genotype exhibited widespread amyloid plaque deposition and tau pathology throughout cortical and cerebellar regions, accompanied by pronounced dementia and motor dysfunction (28). However, because this observation represents a single case, it cannot establish that 129M/M directly increases disease severity. Similarly, among reported F198S cases, the patient with a 129V/V genotype demonstrated faster decline of motor function compared with a patient demonstrating the 129M/V heterozygous genotype (29), suggesting a possible association between codon 129 background and clinical variability in this mutation. Overall, codon 129 appears to modify the phenotypic expression of GSS depending on mutations present, although additional cohort studies are required to determine whether specific codon 129 genotypes consistently influence disease progression or neuropathological distribution.

CONCLUSION

This paper synthesizes findings from a wide range of research to understand mutation-specific trends and shared mechanisms of CJD and GSS. By integrating findings across studies, this review facilitates clearer comparisons of clinical and pathological data, identifies mechanisms that may not be apparent in individual case reports or isolated studies, and provides insights to guide future research.

This review supports prior research demonstrating that mutations in the PRNP gene are central to determining both the disease variant and associated clinical phenotype of familial Creutzfeldt–Jakob disease and Gerstmann–Sträussler–Scheinker syndrome. Specific pathogenic PRNP variants, such as E200K, D178N, and V180I, are associated with differences in the presentation and progression of fCJD. In addition, distinct PRNP mutations associated with GSS contribute to variation in disease presentation, including P102L, G131V, and F198S.

Across the reviewed studies, the codon 129 polymorphism of PRNP emerges as an important disease modifier that contributes to variability in clinical phenotype. However, its effects appear to depend on the specific pathogenic mutation rather than following a universal pattern across prion diseases. In some fCJD and GSS variants, homozygosity for methionine or valine at codon 129 may be associated with rapid disease progression and earlier onset, while heterozygosity may

delay symptom onset and be associated with relatively slower disease progression. The distribution of PrP^{Sc} accumulation may also vary among mutation-specific phenotypes, although the relationship between codon 129 genotype and regional PrP^{Sc} buildup requires further investigation.

However, the reviewed data also reveal important discrepancies and exceptions to simplified genotype–phenotype relationships. For instance, while many D178N-associated cases with specific codon 129 backgrounds demonstrated characteristic clinical courses, certain heterozygous individuals also exhibited severe or short-duration disease, suggesting that the influence of codon 129 may depend on additional genetic, biological, or environmental factors.

Overall, the role of codon 129 polymorphism is best understood as a mutation-dependent disease modifier in prion diseases. Its consistent yet sometimes variable effects across different PRNP mutations highlight how small sequence differences can profoundly impact prion conversion efficiency and neurodegeneration. Future studies integrating larger clinical cohorts, genetic analyses, and epigenetic profiling are essential to clarify how codon 129 influences disease progression.

This review is subject to several limitations that may influence the interpretation of its findings. First, the analysis relies on existing literature, which is predominantly composed of case reports, family-based studies, and small observational cohorts due to the rarity of fCJD and GSS. Consequently, the limited sample sizes restrict the ability to generalize genotype–phenotype associations across broader patient populations. Furthermore, the reviewed studies exhibit substantial clinical heterogeneity, including variation in age at onset, disease duration, clinical presentation, and neuropathological findings. Differences in diagnostic criteria and outcome definitions further complicate direct comparisons across studies. Since the paper does not generate its own primary data, its conclusions are dependent on the accuracy and scope of previously published research. Additionally, the findings are susceptible to ascertainment and publication bias, as studies describing novel or statistically significant observations are more likely to be reported than those with negative or inconclusive results. Finally, because disease phenotype is influenced by multiple genetic and biological factors, it is often difficult to distinguish the independent effects of pathogenic PRNP mutations from those of codon 129 genotype and other potential disease modifiers.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work.

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