The genetics of prion diseases

James A. Mastrianni, MD, PhD

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Abstract: Prion diseases are a rare group of fatal neurodegenerative disorders of humans and animals that manifest primarily as progressive dementia and ataxia. Unique to these diseases is the prion, a misfolded isoform of the prion protein that can transmit disease from cell to cell or host to host by associating with, and transforming, normal prion protein into the misfolded isoform (the pathogenic scrapie-inducing form). Although the majority of cases occur on a sporadic basis, and rarely result from exposure to prions, such as mad cow disease, 10–15% are attributable to the presence of an autosomal dominant mutation of the prion protein gene (*PRNP*). Single base pair changes, or the insertion of one or more multiples of a 24 base pair repeat segment, make up the known sequence alterations of *PRNP* associated with genetic prion disease. The common polymorphic codon 129 of *PRNP* also plays an important and complex role in risk and phenotype of sporadic and genetic prion disease. This review will focus on the clinical and histopathologic features of the genetic prion diseases. Selected mutations will be highlighted as a way to illustrate general phenotype-genotype correlations. ***Genet Med*** **2010:12(4):187–195.**

Key Words: *prion, PRNP, genetic prion disease, familial CJD, GSS, FFI*

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CLINICAL DIAGNOSIS OF PRION DISEASES

Genetic prion diseases constitute a continuum of clinical and pathologic manifestations broadly segregated into three principal phenotypes designated as familial Creutzfeldt-Jakob disease (fCJD), Gerstmann-Sträussler-Scheinker (GSS) syndrome, and familial fatal insomnia (FFI). In addition, a Huntington disease phenocopy known as Huntington disease like-1 (HDL-1) has been described in a family with genetic prion disease (Tables 1 and 2).[1] Although there is considerable overlap in their features, recognizing these phenotypes is useful for diagnosis and care. The diagnosis of genetic prion disease requires a combination of the following:

- Clinical features comprising varying combinations of adult-onset neurologic signs and symptoms, that may include dementia, psychiatric symptoms, motoric incoordination (ataxia, dysarthria), myoclonus (muscle jerks), visual disturbances, weakness and/or spasticity, chorea, stroke-like episodes, seizures, and autonomic disturbances, among other less frequent neurologic signs or symptoms.
- Neuropathologic findings that include spongiform degeneration and astrogliosis diffusely distributed throughout the cortex and deep nuclei of the brain (fCJD); multiple

Table 1 Genetic prion diseases: genes and databases

Gene symbol	Chromosomal locus	Protein name	Locus specific
PRNP	20pter-p12	Major prion protein	Prion protein/ CJD database

Table 2 OMIM entries for genetic prion diseases

123400	Creutzfeldt-Jakob disease (CJD)
137440	Gerstmann-Straussler disease (GSD)
176640	Prion protein (PRNP)
245300	Kuru, susceptibility to
600072	Fatal familial insomnia (FFI)
603218	Huntington disease-like 1 (HDL1)

amyloid plaques to which antiprion protein (PrP) antibodies bind (GSS); and a relative lack of spongiform degeneration and presence of neuronal dropout and gliosis primarily within the thalamus and inferior olivary nucleus of the brain stem (FFI).[2,3]

- Family history consistent with autosomal dominant inheritance, although this may be difficult with some mutations that have variable penetrance, or in the rare case of a de novo mutation.
- A prion protein gene (*PRNP*) disease-causing mutation (see molecular genetic testing, Fig. 1 and Table 3).

Other studies including electroencephalogram (EEG), brain imaging (magnetic resonance imaging [MRI] or positron emission tomography [PET] scans), and examination of cerebrospinal fluid (CSF) may be helpful in supporting the diagnosis, but none is diagnostic on its own. Often such studies are performed to evaluate for other potentially treatable diseases of the central nervous system (see section Differential Diagnosis). It should be emphasized that these tests have been best studied and are most helpful in the diagnosis of nongenetic prion disease (i.e., sporadic CJD). Therefore, reliance on these studies for the diagnosis of genetic prion disease is cautioned.

Electroencephalogram

Characteristic EEG findings of periodic sharp wave complexes (PSWCs), consisting of triphasic or sharp wave bursts every 0.5–2.0 seconds, support the diagnosis of prion disease. Although PSWCs are observed in a small percentage of individuals with genetic prion disease, their presence seems to be highly dependent on the associated causal mutation and resultant clinical phenotype; those mutations that produce a CJD-like clinical phenotype and spongiform degeneration pathology seem more likely to have a positive EEG. Also note that initially, the PSWCs may be unilateral, but with disease progression, they typically spread to both brain hemispheres. In late stages of the disease, the periodic activity may disappear.

Brain imaging

- MRI may show mild to moderate generalized cerebral and cerebellar atrophy at the time of presentation or within a short interval after presentation. T2-weighted images may demonstrate hyperintensity of the basal ganglia.[4]
- Diffusion-weighted MRI has been shown to display greater sensitivity and specificity than T2-weighted imaging. Signal hyperintensity of the basal ganglia (caudate and putamen) or cortical ribbon correlates highly with sporadic CJD.[5,6] A small number of reports suggest similar findings in genetic prion disease, especially those with CJD-like phenotypes. Figure 2 shows the characteristic hyperintensities on diffusion-weighted MRI in a patient with sporadic CJD.
- PET or single photon emission computed tomography scanning seems to be of limited usefulness in the diagnostic evaluation of genetic prion disease, because the findings show nonspecific and diffuse cortical hypometabolic activity, sometimes with frontal predominance. The exception to this is FFI, in which the PET scan may demonstrate a significant and selective reduction in activity within the thalamus, the brain region most affected in that disease.

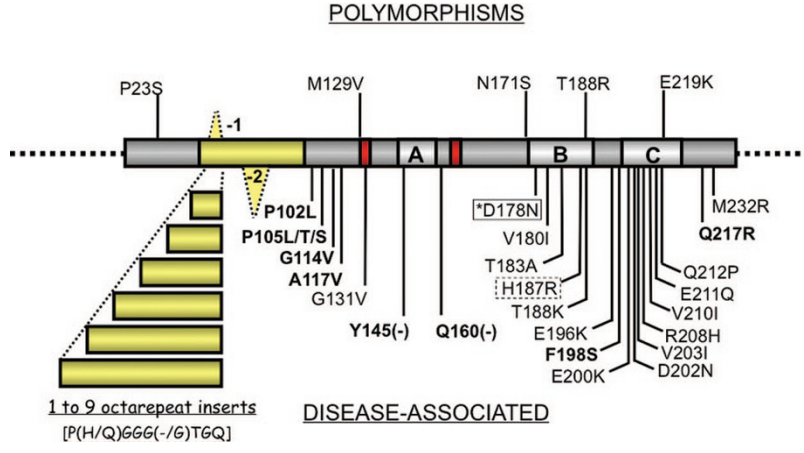

Fig. 1. PRNP gene polymorphisms and mutations. Schematic representation of the PRNP gene, with the major polymorphisms and prion disease-associated mutations. All mutations are associated with a CJD phenotype except those in bold (GSS), solid box (FFI or CJD, depending on codon 129 genotype), and dotted box (CJD phenotype but variable pathology).

Table 3 *PRNP* allelic variants (partial list)

Variant class	DNA Nucleotide change	Protein Amino acid change	Disease phenotype
Normal/Disease modifying	24-bp deletion	Octapeptide deletion	
	385A>G	Met129Val	
	512A>G	Asn171Ser	
	655G>A	Glu219Lys	
Pathologic	24-bp duplications	OPRI (1–9)	Variable[a]
	305C>T	Pro102Leu	GSS
	314C>T	Pro105Leu	GSS
	313C>T	Pro105Ser	GSS
	313C>A	Pro105Thr	?[b]
	350C>T	Ala117Val	GSS
	435T>G	Tyr145Stop	GSS
	478C>T	Gln160Stop	GSS
	532G>A	Asp178Asn	FFI or CJD[c]
	538G>A	Val180Ile	CJD
	547A>G	Thr183Ala	CJD
	560A>G	His187Arg	CJD[d]
	593G>C	Phe198Ser	GSS
	598G>A	Glu200Lys	CJD
	623G>A	Arg208His	CJD
	628G>A	Val210Ile	CJD
	650A>G	Gln217Arg	GSS
	695T>G	Met232Arg[e]	CJD

[a]Presentation and pathology may vary with the number of OPRI.
[b]Clinical presentation consistent with GSS, with exception of very young onset and psychiatric presentation in one member; pathology not available.
[c]The type of phenotype produced depends on allelic codon 129, as described in text.
[d]Presentation variable, but consistent with CJD, whereas pathology is "curly PrP deposits."
[e]See Genetically Related Disorders—M232R not determined directly causal.
GSS, Gerstmann-Sträussler-Scheinker syndrome; FFI, familial fatal insomnia; CJD, Creutzfeldt-Jakob disease.

Cerebrospinal fluid

An isolated increase in CSF protein by ~10% in the absence of a cytological alteration is common in prion disease. Increases in the levels of 14-3-3 protein, neuron specific enolase, and total tau (nonphosphorylated) proteins, which accompany progressive neuronal death, are considered useful markers for nongenetic prion disease; however, because of the generally slower rate of progression of genetic prion disease, these markers seem to be a less consistent feature[7] and should not be relied upon for the evaluation of genetic prion disease. Other conditions that may be accompanied by an elevation in the 14-3-3 protein include herpes encephalitis, stroke, Hashimoto encephalopathy, Alzheimer disease, and on occasion, multiple sclerosis,[8–10] underscoring the need for judicious use of these markers in the diagnostic work up of prion disease.

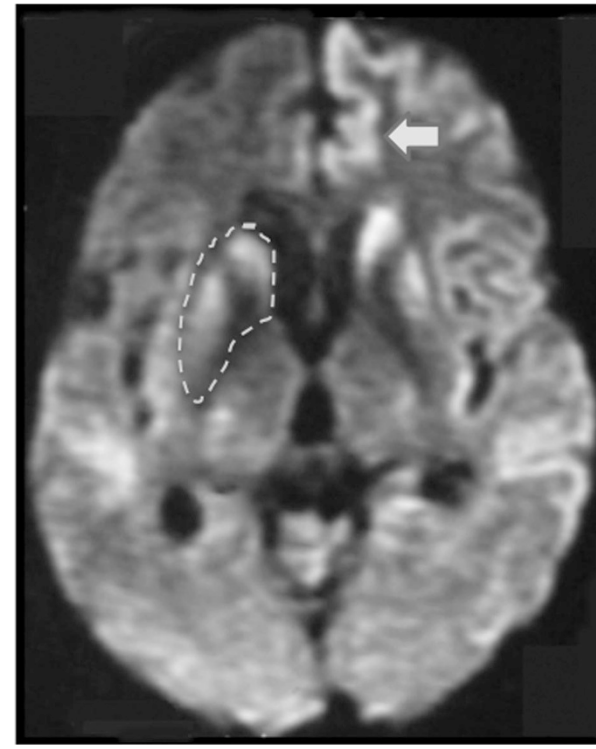

Fig. 2. Diffusion weighted brain MRI of CJD. Hyperintensity of the cortical ribbon (arrow) and basal ganglia (dotted line) are characteristic of sporadic CJD. Although the available data are limited in genetic prion disease, because of its lower incidence, this finding seems to be less common to genetic prion disease.

MOLECULAR GENETIC TESTING

Diagnosis/testing

PRNP is the only gene known to be associated with genetic prion disease. The presence of a *PRNP* mutation is necessary to establish the diagnosis of genetic prion disease in a symptomatic individual.

Genetically related (allelic) disorders

No diseases other than the genetic prion diseases are known to be associated with mutations in *PRNP*. A single case of dementia with Lewy bodies associated with the *PRNP* Met232Arg mutation has been reported, although the causal relationship is uncertain,[11] as more recent reports of this mutation describe a CJD-like phenotype and all cases seem to lack a family history of prion disease.[12,13] Thus, whether the Met232Arg mutation is even causal to prion disease or it represents a modifying polymorphism is still in question.

FAMILIAL PRION DISEASE SUBTYPES

Familial Creutzfeldt-Jakob disease

Progressive confusion and memory impairment occur first, followed by ataxia and myoclonus. Disease onset is typically between 30 and 55 years; however, with certain mutations, disease may present as late as in the ninth decade. The course from disease onset to death ranges from a few months to several years. At end stage disease, the affected individual is generally

bed-bound, mute, and immobile (akinetic), although myoclonic jerks may persist.

The cognitive impairment observed may initially manifest as general confusion or involve a specific cortical function such as language or constructional abilities; however, as the disease progresses, the resultant picture is one of global dementia. Neurobehavioral symptoms may vary considerably and involve psychiatric features such as delusions and hallucinations.

Ataxia may be either truncal or appendicular, manifesting either as an unsteady gait, clumsiness while using their hands to carry out commonly performed tasks (e.g., reaching for objects or feeding oneself), or progressive dysarthria. As disease advances, the ataxia results in repeated falling, necessitating the use of a wheelchair to prevent further injury.

Myoclonus generally, but not always, occurs after cognitive impairment is evident. This may begin focally in a single limb but eventually becomes generalized. "Startle myoclonus" may be elicited by simple acts such as clapping the hands or turning on the room lights. Even if warned of an impending noise, the individual cannot suppress the startle response.

Other neurologic signs and symptoms, such as focal or generalized weakness, rigidity, bradykinesia, tremor, chorea, alien hand syndrome, stroke-like symptoms, visual disturbances, and seizures, among others, have all been reported.

Gerstmann-Straussler-Scheinker syndrome

GSS typically begins within the fourth to sixth decades with the insidious onset of cerebellar dysfunction, manifesting as unsteady gait and/or mild dysarthria. Cognitive dysfunction may not be present early on; however, with progression, bradyphrenia (slowness of thought processing), and clear cognitive impairment eventually becomes evident. Pyramidal involvement, manifesting as spasticity and/or extrapyramidal involvement, resulting in bradykinesia, increased muscle tone, and masked facies, are also common. Psychiatric or behavioral symptoms are atypical. This classic presentation of GSS is known to vary, not only among the several mutations associated with the pathologic features of GSS, but also within family members carrying the same mutation. For instance, in some cases of GSS due to the Ala117Val mutation of *PRNP*, cognitive impairment may be an early or primary feature of the disease, whereas ataxia may be insignificant or absent.[14,15] In all cases, the histopathologic presence of PrP plaque deposits (see below), rather than the clinical features, defines GSS. Despite the variability in clinical features, GSS progresses at a relatively slow, but relentless, pace over the course of three to seven or more years.

Familial Fatal Insomnia

FFI typically presents in midlife (40–50 years) with the onset of insomnia, initially manifest as a mild, then more severe, reduction in overall sleep time. When sleep is achieved, vivid dreams are common. A disturbance in autonomic function then emerges; manifest as elevated blood pressure, episodic hyperventilation, excessive lacrimation, sexual and urinary tract dysfunction, and/or a change in basal body temperature.[16] Signs of brainstem involvement, including decreased ability to gaze upward, double vision, jerky eye pursuit movements, or dysarthric speech, may develop. With continued progression over the next several months, individuals develop truncal and/or appendicular ataxia.

Slowed cognitive processing may develop, as does a variable impairment in memory; however, compared with other more prominent features of disease, cognitive capacity is relatively spared until late in the course. Advance in disease results in progressively greater loss of total sleep time, worsening ataxia, and more profound confusion, leading ultimately to an awake but stuporous state as death approaches. As with other forms of prion disease, debilitation leading to feeding difficulties and loss of airway protection is a common immediate cause of death. FFI typically runs a 12- to 16-month course. It is important to note that insomnia is also common in CJD[17] and has been reported in other genetic forms of prion disease.[18] In addition, the insomnia associated with FFI may be subtle in some individuals and requires polysomnography to document a reduction in total sleep time. However, prominent insomnia as the presenting feature should always raise suspicion for FFI or its nongenetic counterpart, sporadic fatal insomnia (sFI).[16,19]

Neuropathology

The various genetic prion disease syndromes have relatively characteristic neuropathologic changes, including abundant deposition of amyloid plaques that are stained by PrP antibodies in GSS, focal thalamic neuronal loss and gliosis in FFI, and diffusely distributed spongiform change in fCJD (Fig. 3). It is important to note that the neuropathologic findings that characterize the different subtypes may show variations from case to case.[20–22]

GENOTYPE-PHENOTYPE CORRELATIONS

Detailed genotype-phenotype correlations of the various genetic prion disease syndromes can be found elsewhere.[20,21,23] A brief summary of examples follows.

Creutzfeldt-Jakob disease phenotype

Several *PRNP* point mutations have been found in association with the CJD phenotype (Asp178Asn with normal variant Val129, and mutations Val180Ile, Thr183Ala, Glu196Lys, Glu200Lys, Val203Ile, Arg208His, Val210Ile, *Glu211Gln*, Met232Arg; see Table 3).

GSS phenotype

Causal mutations may include Pro102Leu, Pro105Leu, Ala117Val, Gly131Val, Tyr145Stop, Gln160Stop, Phe198Ser, Asp202Asn, Gln212Pro, and Gln217Arg (see Table 3).

FI phenotype

Only one haplotype seems to cause FFI (Asp178Asn + normal variant M129).

Phenotype Variations

His187Arg

Early onset, long duration, and a presentation that includes neuropsychiatric symptoms and features of frontotemporal dementia have been reported in a large family with the His187Arg mutation,[24] although another family was reported with more typical signs of dementia, ataxia, myoclonus, and seizures.[25]

Octapeptide repeat insertions

Insertional mutations are associated with a variable clinical and pathologic phenotype. These insertions all lie within an unstable region of *PRNP* that is rich in proline, glycine, and glutamine (see section Molecular Genetics). Normal *PRNP* alleles have one nonapeptide followed by four octapeptide repeat sequences each of which is comprised the following amino acids: Pro-(His/Gln)-Gly-Gly-Gly-(-/Trp)-Gly-Gln. Because the nucleotide sequence encoding the octapeptide may

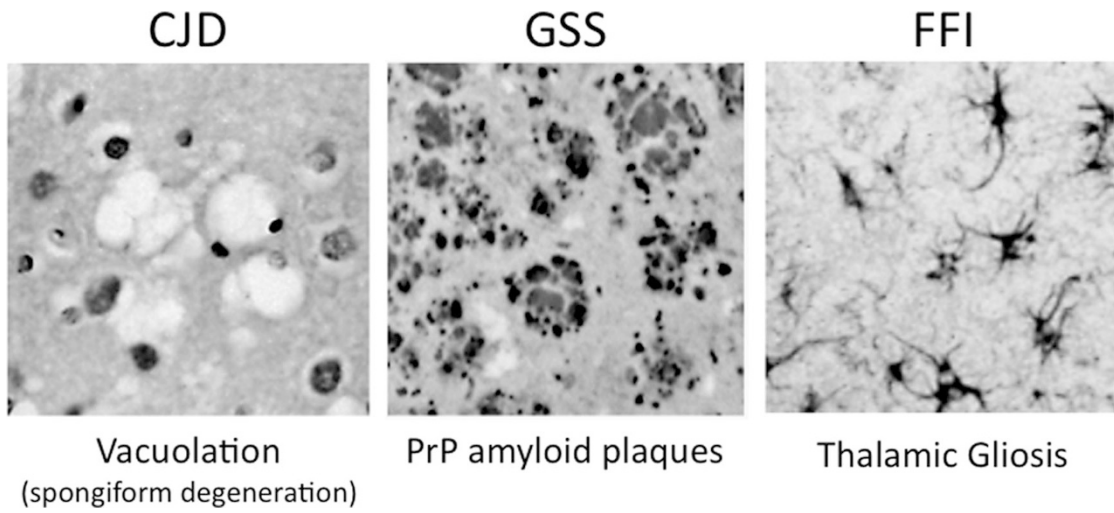

Fig. 3. Histopathologic features of the three major subtypes of genetic prion diseases.

vary, the repeat is described typically as an octapeptide rather than as a 24-nucleotide repeat.

One to nine additional octapeptide repeat insertions (OPRI) have been detected in patients with prion disease. As a group, they are notable for a significant phenotypic variability, including a variable rate of progression of dementia, sometimes with psychiatric features, with or without cerebellar ataxia and/or myoclonus, and a histopathology that ranges from minimal features to widespread spongiform degeneration with PrP plaque deposits.[26,27] Although this variability is reported to be greater among the different insertions, it has also been observed among members of the same pedigree.[28]

- OPRI of 3 or less have been reported in small numbers, with a clinical and histopathologic phenotype similar to CJD, raising questions as to whether these are true autosomal dominant mutations with variable penetrance or incidental polymorphisms in cases of sCJD.
- Although variability is high with these mutations, in general, the longer the OPRI, the earlier the disease onset (35 vs. 45 years) and the higher the likelihood that PrP amyloid deposits will be a histological feature.[27]
- In some examples of OPRI, a presymptomatic phase, which includes aggressiveness, hypersexuality, and criminal behavior, suggesting frontal lobe involvement, has been recognized.[29]
- A HDL-1 phenotype was reported in a family with an 8-OPRI.[1] Interestingly, another individual was reported with the HDL-1 phenotype but later found to be a member of the largest known 6-OPRI kindred, further supporting the variable phenotype observed with OPRI mutations, in addition to the importance of genetic testing in neurodegenerative disease.[30]

Normal/disease-modifying variants

Codon 129

The common normal variant at codon 129 of *PRNP* (385A>G) codes for either methionine (Met; 129M) or valine (Val; 129V). Approximately 50% of the Caucasian population is homozygous at this variation for either Met (40%) or Val (10%), although an average of 70% of individuals with sporadic CJD are homozygotes.[31,32] In variant CJD, which results from exposure to bovine spongiform encephalopathy (BSE) (i.e., mad cow disease), 100% of affected individuals are 129M homozygotes.

- In selected cases of genetic prion disease, when the normal allele carries the same polymorphic codon 129 as the mutated allele, the onset of disease and its course is shorter compared with those that are 129MV heterozygotes.[28,33]
- For alleles with the Asp178Asn mutation, the presence of 129M vs. 129V modifies the phenotype of disease: when it is 129V, the phenotype is almost always typical fCJD; when it is 129M, the phenotype is almost always FFI; and even in nonfamilial forms of CJD, the Met129Val variant seems to affect disease phenotype such that 129MM individuals most often present with dementia and a more rapid disease course, whereas most 129VV individuals and ~25% of 129MV individuals display ataxia at onset and a slower disease course.[34]

Codon 219

The Glu219Lys variant has been reported in roughly 6% of the Japanese population, but is absent in CJD, suggesting a protective effect.[35] This was confirmed in cell culture[36] and transgenic mouse studies that found PrP-219K was not converted to PrP^{Sc} and it also inhibited the conversion of coexpressed wild-type PrP.[37]

Codon 127

Recently, a novel Gly127Val polymorphism was identified in a selective population in New Guinea, where kuru, a prion disease transmitted by cannibalism, was described. It is proposed that this polymorphism, in addition to codon 129, reduces the relative risk to developing kuru in exposed individuals.[38]

Penetrance

The Glu200Lys and Val210Ile mutations of *PRNP* are commonly associated with a variable, but generally age-dependent penetrance, such that the older the individual, the greater likelihood of manifesting the disease.[39] Thus, it is not uncommon to encounter a situation in which the parents and other relatives of an affected individual may be unaffected but have a *PRNP* mutation.

Most other *PRNP* point mutations demonstrate complete penetrance.

Anticipation

Genetic anticipation has not been demonstrated.

Nomenclature

Spastic pseudosclerosis is an older term used to describe a more fulminant course of CJD, because it seemed to have features suggestive of multiple sclerosis, with spasticity of gait and limbs.

Heidenhain variant is a term used to describe a specific presentation of CJD that occurs in about 10% of nongenetic forms. It begins with visual symptoms that may manifest as visual loss, blurring, and visual distortions (e.g., bending in the walls), related to the early involvement of the occipital lobes.

Prevalence

The general worldwide yearly incidence of genetic and nongenetic prion disease is approximately one case per million. The genetic forms of prion disease represent ~10% of the total number of prion disease cases.

The most common disease-associated mutations of *PRNP* are Glu200Lys, the largest focus being present in the Middle East (Libyan Jews) and Eastern Europe (Slovakia), and Asp178Asn, which is found worldwide. Other mutations are relatively rare.[40]

In Italy, nearly 18% of all cases of prion disease had a *PRNP* mutation, with Val210Ile and Glu200Lys being the most common mutations observed.[41]

DIFFERENTIAL DIAGNOSIS

Nongenetic prion diseases

About 10–15% of prion diseases are genetically transmissible, whereas the remaining occur spontaneously from unknown risk factors (~90%) or are acquired through exposure to prions; these include sporadic CJD (sCJD), iatrogenic CJD (iCJD), variant CJD (vCJD), and sporadic fatal insomnia (sFI). Kuru, a prion disease associated with the practice of cannibalism in a primitive culture in New Guinea, is primarily of historical significance.

Sporadic CJD

The clinical and pathologic features of sCJD are the same as in fCJD; however, the duration of disease is typically much shorter (on average, ≤6 months) and the age at onset is later (typically, between 60 and 70 years).

Sporadic FI

The phenotype is the same as in FFI, including age at onset and duration of disease[19,42]; sFI is much less common than FFI, with only a handful of cases thus far reported.

Iatrogenic CJD

This type of prion disease results from the exposure to a biological extract or tissue contaminated with prions. Such sources have included injections of human growth hormone (used before 1980), improperly decontaminated depth electrodes previously used in individuals with CJD, transplantation of corneas obtained from individuals with CJD, dura mater grafts, and some neurosurgical procedures.[43]

Variant CJD

Variant CJD represents a relatively new strain of CJD acquired by ingestion of beef or beef products contaminated with BSE. The typical clinical picture is that of a young adult or teen who develops behavioral changes (apathy and depression) and/or pain in the lower extremities that eventually lead to a progressive dementia with ataxia and myoclonus.[44] The course is about 1.5 years. The EEG is often diffusively slow rather than periodic, and the 14-3-3 protein is typically negative. Neuropathology reveals spongiform change spread diffusely throughout the brain and dense amyloid plaque deposition surrounded by a halo of vacuolation, described as "florid plaques."[45]

Other neurodegenerative diseases

Prion disease should always be considered in an individual with progressive cognitive decline, either in isolation or when combined with a movement disorder, especially ataxia. The rapidity of progression may be a helpful clue; however, many genetic prion diseases progress slowly, especially those due to OPRI mutations and those associated with GSS. These slowly progressive cases may be easily confused with several other neurodegenerative diseases, including Alzheimer disease, dementia with Lewy bodies, Huntington disease, progressive supranuclear palsy, the inherited ataxias, and the frontotemporal lobar dementias (FTLD), including progressive subcortical gliosis, dementia with motor neuron disease, Pick disease, and FTD with parkinsonism (chromosome 17-linked FTDP),[46] inclusion body myopathy with Paget disease of bone and/or frontotemporal dementia, *CHMP2B*-related frontotemporal dementia, and *GRN*-related frontotemporal dementia. Thus, when prion disease is being entertained, these conditions should also be considered, and when any of these diagnoses are being entertained, a detailed family history should be obtained, and *PRNP* gene analysis should be considered.

Other CNS conditions

Autoimmune diseases such as Hashimoto thyroiditis with related encephalopathy, paraneoplastic syndromes such as limbic encephalitis, and/or systemic CNS vasculitides, multiple sclerosis, toxins (heavy metals, including bismuth), Whipple disease, and metabolic abnormalities, must also be considered.

MANAGEMENT

Evaluations after initial diagnosis

To establish the extent of disease in an individual diagnosed with genetic prion disease, physical examination, with a focus on the neurologic features of cognition, motor function, and coordination is recommended. This will provide a gauge as to the rate of disease progression that will aid the family in planning for the future.

Treatment of manifestations

Therapy is aimed at controlling symptoms that may cause discomfort.

- If present, seizures may be treated with general antiepileptic drugs including diphenylhydantoin or carbamazepine.
- Myoclonus can be mitigated by low doses of clonazepam.
- Issues related to dysphagia are often difficult to resolve. Because the disease is terminal, families are often faced with the difficult decision of whether to place a permanent feeding tube. The timing of this decision differs depending on the type of prion disease; GSS and the ataxic presentation of CJD tend to develop swallowing difficulties earlier in the disease process, compared with CJD or FFI.
- Severe psychiatric symptoms that may include hallucinations and/or delusions are best managed by small doses of

atypical antipsychotics, such as quetiapine; however, families should be cautioned that these drugs are associated with an early and unexpected death in older individuals with dementia.

Evaluation by a social worker is mandatory to assist the family in management planning, because many decisions are required during the course of disease and at the end of the disease process.

Referral of cases for autopsy to major centers equipped to perform them is another important aspect in the handling of cases of prion disease. This not only serves to provide the family with much needed information and confirmation of disease but also assists in an ongoing program of prion disease surveillance.

Therapies recently investigated

Government-sponsored clinical trials in the United States and the United Kingdom recently tested quinacrine, an antimalarial agent that showed promise in tissue culture, although results in rodents were less convincing. The data released at this time do not support it to be of clinical benefit against sporadic CJD.

Monitoring disease

Affected individuals are examined at regular intervals for complications related to swallowing difficulties, infections, and other disease manifestations.

Other issues

Individuals with genetic prion disease do not need to be quarantined. Although all prion diseases are potentially transmissible through ingestion or injection of prion-affected tissue, patients are not contagious by typical means of close contact with affected individuals. However, it is advisable that body fluids of symptomatic individuals be handled as biohazard waste.

Antiviral therapies have been tested and anecdotal reports do not support their efficacy. In rodent studies, amphotericin B, pentosan polysulfate, and various other agents displayed promise when administered before challenging animals with infectious prions; however, no successful clinical results have been reported. Anectodal reports of a slowing of disease progression in patients with CJD who received pentosan polysulfate intrathecally, orally administered tacrolimus, or orally administered tetracycline antibiotics, have surfaced in recent years, although no clinical trial has been conducted to demonstrate benefit. The rarity of cases makes large scale clinical trials difficult.

Genetic counseling

Genetic prion disease is inherited in an autosomal dominant manner. Thus, each child of an individual with a disease-causing *PRNP* mutation has a 50% chance of inheriting the mutation. Most individuals diagnosed with genetic prion disease have an affected parent, although the rare possibility of a de novo gene mutation must also be considered. Further, because penetrance seems to be reduced in some mutations (especially Glu200Lys), the parent with a disease-causing mutation may be unaffected while a child is affected.

Related genetic counseling issues

Pretest counseling for families of symptomatic individuals with no family history of neurologic disease is useful to better prepare families to make informed decisions regarding genetic test results.[47]

Testing of at-risk asymptomatic adults

At-risk asymptomatic adult family members may seek testing to make personal decisions regarding reproduction, financial matters, and career planning. Others may have different motivations including simply the "need to know." Testing of at-risk asymptomatic adults is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. When testing at-risk individuals for genetic prion disease, an affected family member must be tested first to confirm the molecular diagnosis in the family. Testing of asymptomatic at-risk adult family members usually involves pretest interviews in which the motives for requesting the test, the individual's knowledge of genetic prion diseases, the possible impact of positive and negative test results, and neurologic status. Those seeking testing should be counseled about possible problems that they may encounter with regard to health, life, and disability insurance coverage; employment and educational discrimination; and changes in social and family interaction. Other issues to consider are implications for the at-risk status of other family members. These include the public health issues that affect family members of a patient with genetic prion disease, specifically their restriction from blood and organ donation. Informed consent should be procured and records kept confidential. Individuals with a positive test result need arrangements for long-term follow-up and evaluations.

Testing of at-risk individuals during childhood

Consensus holds that individuals younger than 18 years who are at risk for adult-onset disorders should not have testing in the absence of symptoms. The principal arguments against testing asymptomatic individuals during childhood are that it removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications. In addition, no preventive treatment for prion diseases is available.

Molecular genetics

Normal allelic variants

The normal *PRNP* gene has a coding region of 756 nucleotides in two exons. Several allelic variants not associated with autosomal dominant linkage to prion disease have been detected; however, these variants may play a role in altering risk and phenotype of disease from either sporadic or genetic forms of prion disease (see Table 3). They include Met129Val (see section Genotype-Phenotype Correlations), Glu219Lys, Asn171Ser, and a deletion of a single octapeptide repeat segment.[48] Although these variants do not seem to independently promote disease, homozygosity at codon 129 seems to increase disease susceptibility, and depending on the substitution, this polymorphic site seems to affect the phenotype of disease. The Glu219Lys variant has been reported as protective, although this change is currently limited to the Japanese population.[49]

Normal alleles have a repeat region between amino acid residues 51 and 91 comprising one nonapeptide unit that begins at residue 51 and encodes the following nine amino acids: Pro-Gln-Gly-Gly-Gly-Gly-Trp-Gly-Gln. This is followed by four octapeptide units beginning at residue 60 encoding the following eight amino acids: Pro-His-Gly-Gly-Gly-Trp-Gly-Gln. The octapeptide units can be unstable and are duplicated in pathologic allelic variants. Because the nucleotide sequence encoding the octapeptide units can vary slightly, the specific sequences for normal and pathologic alleles in this region are often not specified.

Pathologic allelic variants

A host of pathologic allelic variants (see *Genotype-Phenotype Correlations*) are known. Three major types of pathogenic mutations have been described.

- Nucleotide substitutions that result in an amino acid substitution (see Table 3). All of the mutations associated with pathology are in-frame heterozygous mutations with the exception of five examples of individuals homozygous for the Glu200Lys mutation, who developed disease at a somewhat earlier age.[50]
- An insertion (also called a duplication) of one or more octapeptide repeat segment(s), which results in an extended PrP. These OPRI mutations involve the insertion of one or more octapeptide repeat segments between codons 51 and 91. Each OPRI adds 24 nucleotides to the gene or 8 amino acids to the protein. One to nine additional OPRI (Pro-His-Gly-Gly-Gly-Trp-Gly-Gln) have been associated with disease.
- The generation of an early stop signal that results in a truncated PrP. Two known substitutions that result in an early stop signal include Tyr145Stop and Gln160Stop.

Normal gene product

The prion protein is translocated into the endoplasmic reticulum (ER) during translation, as a 253-amino acid protein. Once within the ER lumen, the first 23 amino acids (which constitute a signal sequence) are cleaved, as are the last 23 amino acids, which signal the attachment of a glycosyl-phosphatidylinositol (GPI) anchor, by which the protein is attached to the plasma membrane. Two asparagine-linked glycosylation sites are present. The normal function of the protein is unknown, although roles in synapse formation, copper delivery to cells, and cell signaling have been proposed. Two major isoforms of the prion protein exist: the nonpathogenic (cellular) form (PrP^{C}) and the pathogenic (scrapie-inducing) form (PrP^{Sc}).[51] Although the amino acid sequence is the same in the two, their biochemical properties differ: PrP^{C} is α-helical, PrP^{Sc} is at least 40% β-pleated sheet; PrP^{C} is soluble in nondenaturing detergents, whereas PrP^{Sc} is insoluble; PrP^{C} is completely degraded by proteases, whereas PrP^{Sc} has a relative resistance to proteases.

Abnormal gene product

The normal three-dimensional conformation of the protein product is presumably destabilized by the introduction of a pathogenic mutation, which enhances the propensity for the protein to acquire the PrP^{Sc} conformation. PrP^{Sc} then behaves as a conformational template that complexes with nonpathogenic PrP^{C} to convert it to additional PrP^{Sc}. The manner in which the accumulation of PrP^{Sc} induces cytotoxicity is not yet known.

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