U.S. National Library of Medicine
National Center for Biotechnology Information

**NLM Citation:** Zerr I, Schmitz M. Genetic Prion Disease. 2003 Mar 27 [Updated 2021 Jan 7]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
**Bookshelf URL:** https://www.ncbi.nlm.nih.gov/books/


# Genetic Prion Disease

Inga Zerr, MD[1] and Matthias Schmitz, MD[1]

Created: March 27, 2003; Updated: January 7, 2021.

## Summary

### Clinical characteristics

Genetic prion disease generally manifests with cognitive difficulties, ataxia, and myoclonus (abrupt jerking movements of muscle groups and/or entire limbs). The order of appearance and/or predominance of these features and other associated neurologic and psychiatric findings vary. The three major phenotypes of genetic prion disease are genetic Creutzfeldt-Jakob disease (gCJD), fatal familial insomnia (FFI), and Gerstmann-Sträussler-Scheinker (GSS) syndrome. Although these phenotypes display overlapping clinical and pathologic features, recognition of these phenotypes can be useful when providing affected individuals and their families with information about the expected clinical course. The age at onset typically ranges from 50 to 60 years. The disease course ranges from a few months in gCJD and FFI to a few (up to 4, and in rare cases up to 10) years in GSS syndrome.

### Diagnosis/testing

The diagnosis of genetic prion disease is established in a proband with suggestive findings and a heterozygous *PRNP* pathogenic variant identified by molecular genetic testing.

### Management

*Treatment of manifestations:* No treatment of the underlying cause of genetic prion disease is available. Supportive care by a multidisciplinary team of specialists including neurologists, psychiatrists, physical therapists, occupational therapists, speech and language therapists, and social workers is recommended.

*Surveillance:* Because of very rapid disease progression, close periodic monitoring by the multidisciplinary team is needed, typically every 14 days to evaluate needs for symptomatic treatment.

**Author Affiliation:** 1 Department of Neurology, University Medical School, Göttingen, Germany; Email: ingazerr@med.uni-goettingen.de; Email: matthias.schmitz@med.uni-goettingen.de.

## Genetic counseling

Genetic prion disease is inherited in an autosomal dominant manner. Some individuals diagnosed with genetic prion disease may have a parent who is heterozygous for a *PRNP* pathogenic variant (some of whom may be asymptomatic because of reduced penetrance). Other individuals with genetic prion disease may have the disorder as the result of a *de novo PRNP* pathogenic variant. Each child of an individual with a *PRNP* pathogenic variant has a 50% chance of inheriting the variant. Although predictive testing (i.e., testing of asymptomatic at-risk adults) is possible, the capabilities and limitations of predictive testing as well as possible socioeconomic and medical care issues should be discussed in the context of formal genetic counseling prior to testing. Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years) is considered inappropriate.

# *GeneReview* Scope

| Genetic Prion Disease: Included Phenotypes |
| --- |
| • Genetic Creutzfeldt-Jakob Disease (genetic CJD) [1]<br>• Fatal familial insomnia (FFI)<br>• Gerstmann-Sträussler-Scheinker syndrome (GSS) |

*1.* May also be referred to as familial CJD

# Diagnosis

## Suggestive Findings

Genetic prion disease should be suspected in individuals with the following clinical, laboratory, and imaging findings and family history.

### Clinical

Genetic prion disease is a progressive neurodegenerative syndrome with rapid evolution of clinical signs (which reflect involvement of various neuroanatomic structures) – typically, dementia in combination with the following developing within a few months or (rarely) a few years:

- Extrapyramidal/pyramidal involvement
- Ataxia
- Myoclonus

In fatal familial insomnia (FFI) early autonomic disturbances and weight loss are frequent.

### Laboratory

Cerebrospinal fluid analysis may be abnormal with high levels of 14-3-3 protein and protein tau.

Abnormally conformed prion protein using aggregation assays (RT QuIC) is typically positive in genetic Creutzfeldt-Jakob disease (gCJD), but not always in FFI or Gerstmann-Sträussler-Scheinker syndrome (GSS).

### Imaging

**MRI**

- In some individuals with genetic CJD, MRI may display high signal abnormalities in the basal ganglia (caudate nucleus) and cortical areas, mostly in diffusion-weighted imaging (DWI), but also $T_2$-weighted-fluid-attenuated inversion recovery (FLAIR) images.

- In individuals with FFI and GSS, MRI is typically not suggestive.

**FDG PET** (typically displaying hypometabolism in the thalamic areas) may be helpful in individuals FFI.

### Family History

Family history is consistent with autosomal dominant inheritance (i.e., multiple affected family members in successive generations or a single affected family member). Absence of a known family history does not preclude the diagnosis.

## Establishing the Diagnosis

The diagnosis of genetic prion disease is established in a proband with suggestive findings and a heterozygous *PRNP* pathogenic (or likely pathogenic) variant identified by molecular genetic testing [Ladogana & Kovacs 2018] (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *PRNP* variant of uncertain significance does not establish or rule out the diagnosis of the disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing).

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of genetic prion disease has not been considered may be more likely to be diagnosed using genomic testing (see Option 2).

### Option 1

**Single-gene testing**. Sequence analysis of *PRNP* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Typically, if no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, to date such variants have not been identified as a cause of this disorder.

**Note: Targeted analysis for pathogenic variants** can be performed first in individuals of European ancestry; the following five common variants account for approximately 85% of the *PRNP* pathogenic variants in this population (see Table 4 for details):

- P102L (c.305C>T; p.Pro102Leu)
- D178N (c.532G>A; p.Asp178Asn)
- V180I (c.538G>A; p.Val180Ile)
- E200K (c.598G>A; p.Glu200Lys)
- V210I (c.628G>A; p.Val210Ile)

**A multigene panel** that includes *PRNP* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or

custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

### Option 2

**Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

**Table 1.** Molecular Genetic Testing Used in Genetic Prion Disease

| Gene [1] | Method | Proportion of Probands with a Pathogenic Variant [2] Detectable by Method |
|---|---|---|
| *PRNP* | Sequence analysis [3] | 100% [4] |
| | Gene-targeted deletion/duplication analysis [5] | None reported |

*1.* See Table A. Genes and Databases for chromosome locus and protein.
*2.* See Molecular Genetics for information on variants detected in this gene.
*3.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
*4.* Schmitz et al [2017] and Takada et al [2017] include the five pathogenic variants of targeted sequence analysis and the octapeptide insertion/duplication/deletion variants that are detectable by sequence analysis (see Table 4).
*5.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

# Clinical Characteristics

## Clinical Description

Genetic prion disease generally manifests with cognitive difficulties, ataxia, and myoclonus (abrupt jerking movements of muscle groups and/or entire limbs). The order of appearance and/or predominance of these features and other associated neurologic and psychiatric findings vary. The three major phenotypes of genetic prion disease are genetic Creutzfeldt-Jakob disease (gCJD), fatal familial insomnia (FFI), and Gerstmann-Sträussler-Scheinker (GSS) syndrome. Although these phenotypes display overlapping clinical and pathologic features, recognition of these phenotypes can be useful when providing affected individuals and their families with information about the expected clinical course. The age at onset typically ranges from ages 50 to 60 years. The disease course ranges from a few months in gCJD and FFI to a few (up to 4, and in rare cases up to 10) years in GSS syndrome.

Table 2 provides information on the frequency of neurologic features in the most frequent genetic prion disease phenotypes that emerge during the disease course. While some *PRNP* pathogenic variants are associated with specific neuropathologic phenotypes, individuals in the same family who are heterozygous for the same *PRNP* variant may develop distinct clinicopathologic phenotypes [Cracco et al 2018].

**Table 2.** Select Features of Genetic Prion Disease by Phenotype and *PRNP* Pathogenic Variant

| Feature | | % of Persons w/Feature by Phenotype & *PRNP* Variant | | | |
|---|---|---|---|---|---|
| | | gCJD | | FFI | GSS |
| | | E200K | V210I | D178N | P102L |
| **Dementia** | | 95% | 92% | 96% | 62% |
| **Ataxia** | | 100% | 100% | 82% | 100% |
| **Myoclonus** | | 85% | 92% | 89% | 25% |
| **Extrapyramidal** | | 65% | 92% | 82% | 50% |
| **Pyramidal** | | 70% | 71% | 79% | 75% |
| **Visual/Cortical blindness** | | 70% | 85% | 79% | |
| **Other characteristic features** | **Dysarthria** | Yes | Yes | Yes | Yes |
| | **Sleep disturbances** | Yes | | Yes | Yes |
| | **Sensory symptoms** | | Yes | | Yes |
| | **Weight loss** | Yes | | Yes | |
| | **Hyperhidrosis** | | | Yes | |

Adapted from Krasnianski et al [2016] (based on 108 affected individuals ascertained by the CJD Surveillance Unit in Göttingen, Germany, from 1993 to 2005)

## Genetic Creutzfeldt-Jakob Disease (gCJD)

Genetic prion disease caused by pathogenic variants E200K and V210I frequently resembles the phenotype of sporadic CJD (see Differential Diagnosis). Typical disease onset is in the sixth decade; after a nonspecific prodromal phase with dizziness, fatigue, blurred vision, depressive mood, and weight loss, the disease starts frequently with cognitive decline that progresses over several weeks. Within a few months of progressive neurologic decline, affected individuals become bedridden and akinetic/mute. The advanced disease stage is characterized by rapid involuntary muscle jerks (myoclonus), muscle stiffness (either rigidity or spasticity), and ataxia. The median survival following disease onset is six months.

## Fatal Familial Insomnia (FFI)

A prodromal phase with marked autonomic disturbances, hyperhidrosis, weight loss, and sleep disturbances is common. Polysomnography shows complete disruption of the physiologic EEG sleep pattern.

After a nonspecific stage as described for gCJD, affected individuals develop progressive dementia, ataxia, muscle rigidity and involuntary movements. At the end stage of the disease, the clinical manifestations are similar to those of other genetic prion disease phenotypes.

The median age at onset is between 50 and 60 years. The median survival is 16 months. See Genotype-Phenotype Correlations for information on a variant associated with a shorter disease course.

## Gerstmann-Sträussler-Scheinker (GSS) Syndrome

The typical clinical manifestations are a rapidly progressive cerebellar syndrome with ataxia at onset followed by cognitive decline and other neurologic signs within a few weeks, or at most a few months.

The typical age at onset, earlier than in the other genetic prion diseases, is early in the sixth decade (51 years) with disease duration typically up to four years.

Tesar et al [2019], who used cluster analysis to address the clinical heterogeneity of GSS syndrome, reported the following four clinical phenotypes:

- Typical GSS syndrome with early ataxia, late dementia, and long disease duration (up to 4 years)
- GSS syndrome beginning with areflexia and paresthesias, and later ataxia and dementia
- Pure dementia GSS syndrome with early onset (age 35 years) with predominant dementia and late ataxia
- Creutzfeldt-Jakob disease-like GSS syndrome with dementia and ataxia at onset and rapid disease progression

## Genotype-Phenotype Correlations

Although some *PRNP* pathogenic variants are associated with specific neuropathologic phenotypes (see Table 2), evidence also suggests that heterozygotes for the same variant in the same family may develop distinct clinicopathologic phenotypes [Cracco et al 2018].

Note that the phenotype may be modified by the presence of the polymorphic codon 129 (p.Asp178Asn) in *cis* configuration with the *PRNP* variant. The phenotype in individuals with the p.Asp178Asn pathogenic variant typically depends on which variant – Met129 or Val129 – is in *cis* configuration with the *PRNP* variant. In general, the onset of genetic prion disease is earlier and its course shorter (11 months) in individuals homozygous for Met129 compared to either heterozygotes or homozygotes for Val129, in whom the phenotype is usually typical genetic CJD. See Table 4.

## Penetrance

The penetrance for genetic prion disease in general is assumed to be 100%; however, only a limited number of studies have been performed to address this issue.

The penetrance for the E200K variant (which has been studied more extensively than for other variants) was 60%-70% in Italian and Slovak families [D'Alessandro et al 1998, Mitrová & Belay 2002] and 100% in Libyan Jewish families [Spudich et al 1995].

## Prevalence

Epidemiologic studies utilizing reports of prion disease from centers around the world are frequently consistent with respect to the prevalence of genetic prion disease, as 15% of all individuals with newly diagnosed prion disease have genetic prion disease (i.e., are heterozygous for a *PRNP* pathogenic variant).

The E200K variant has been identified in populations worldwide, including in Slovakia, in Jewish families from Libya, Chile, and Tunisia, and in individuals of non-Jewish origin in other countries. Studies of ancestral origins by microsatellite markers flanking *PRNP* on chromosome 20p12-pter and an intragenic single-nucleotide polymorphism at *PRNP* codon 129 demonstrated that the E200K variant may have originated from a single event, potentially in Spain, and spread to Libya, Tunisia, Chile, and Italy. Families from Slovakia and Poland show similar linked genetic markers as well as those from Germany, Austria, and Sicily; however, in affected individuals from Japan, different linked genetic markers have been identified, suggesting the independent origin of the variants [Lee at al 1999, Ladogana & Kovacs 2018].

# Genetically Related (Allelic) Disorders

No phenotypes other than those of genetic prion disease that are discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PRNP*.

# Differential Diagnosis

Because of the progressive neurologic decline, the range of neurologic signs, and the heterogeneous presentation of genetic prion disease, the differential diagnosis is broad and needs to include other hereditary neurodegenerative disorders as well as a variety of acquired disorders. Because potential treatment options depend on identification of the underlying cause, autoimmune and paraneoplastic disorders need to be considered (see Table 3).

**Table 3.** Disorders Potentially Associated with Rapid Progression of Interest in the Differential Diagnosis of Genetic Prior Disease

| Etiology | Disorder/Comment | Gene(s) |
|---|---|---|
| **Hereditary neurodegenerative disorders** | *CSF1R*-related adult-onset leukoencephalopathy w/axonal spheroids & pigmented glia | *CSF1R* |
| | Dementia w/Lewy bodies (OMIM 127750) | *GBA1* (*GBA*)<br>*SNCA*<br>*SNCB* |
| | Familial Alzheimer disease (See Alzheimer Disease Overview. [1]) | *APP*<br>*PSEN1*<br>*PSEN2* |
| | Frontotemporal dementia (e.g., ALS/FTD, *CHMP2B*-FTD, *GRN*-FTD, IBMPFD) | *C9orf72* [2]<br>*CHMP2B*<br>*FUS*<br>*GRN*<br>*HNRNPA1*<br>*HNRNPA2B1*<br>*TARDBP* [3]<br>*VCP* |
| | Hereditary ataxia (e.g., SCA1, SCA2, SCA3, SCA6, SCA7, SCA8) [4] | *ATXN1*<br>*ATXN2*<br>*ATXN3*<br>*ATXN7*<br>*ATXN8*<br>*CACNA1A* |
| | Huntington disease | *HTT* |
| | Pick disease (OMIM 172700) | *MAPT* [5]<br>*PSEN1* |
| | Progressive supranuclear palsy (OMIM 601104) | *MAPT* [5] |
| **Autoimmune** | e.g., Hashimoto thyroiditis w/related encephalopathy, multiple sclerosis, antibody-mediated dementia/encephalopathy, CNS lupus, acute disseminated encephalomyelitis | |
| **Iatrogenic** | e.g., medication toxicity (e.g., lithium, methotrexate, chemotherapy), illicit drug use | |
| **Infectious** | e.g., viral encephalitis (incl herpes simplex virus), HIV dementia, progressive multifocal leukoencephalopathy | |
| **Metastases/ Neoplasm related** | e.g., paraneoplastic diseases-limbic encephalopathy, metastases to CNS, primary CNS lymphoma | |
| **Systemic/Seizures/ Structural** | e.g., sarcoidosis, epilepsy, nonconvulsive status epilepticus | |
| **Toxic-metabolic** | e.g., heavy metals (incl bismuth), electrolyte disturbances (sodium, calcium, magnesium, phosphorus), endocrine abnormalities (thyroid, parathyroid, adrenal), extrapontine myelinolysis | |

*Table 3. continued from previous page.*

| Etiology | Disorder/Comment | Gene(s) |
|---|---|---|
| **Vascular/Ischemia** | e.g., multi-infarct, thalamic or callosum infarcts, cerebral amyloid angiopathy | |

Adapted from Geschwind [2016], Table 7-4: Partial Differential Diagnosis for Rapidly Progressive Dementias by Etiologic Category
ALS = amyotrophic lateral sclerosis; CNS = central nervous system; FTD = frontotemporal dementia; HIV = human immunodeficiency virus; IBMPFD = inclusion body myopathy associated with Paget disease of bone and/or frontotemporal dementia
*1.* Listed genes are associated with early-onset familial Alzheimer disease (EOFAD): Alzheimer disease that occurs in multiple members of a family with a mean onset usually before age 65 years. EOFAD represents fewer than 2% of Alzheimer disease cases. Late-onset familial Alzheimer disease (age >60-65 years), representing 15%-25% of Alzheimer disease cases, is thought to be a complex disorder possibly involving multiple susceptibility genes (see Alzheimer Disease Overview).
*2.* See C9orf72-ALS/FTD.
*3.* See *TARDBP*-ALS-FTD.
*4.* The hereditary ataxias are a large group of autosomal dominant, autosomal recessive, and X-linked disorders characterized by slowly progressive incoordination of gait and often associated with poor coordination of hands, speech, and eye movements; see Hereditary Ataxia Overview for molecular genetic and clinical information.
*5.* See *MAPT*-FTD.

For a detailed review of disorders to consider in an individual with rapidly progressive dementia, see Geschwind [2016].

## Other Prion Diseases

**Sporadic CJD** (i.e., CJD of unknown cause diagnosed in an individual with a negative family history and no pathogenic *PRNP* variant) is the most common human prion disease. Sporadic CJD is generally regarded as a spontaneous neurodegenerative illness. While genetic CJD caused by the *PRNP* variants E200K and V210 can be clinically almost indistinguishable from sporadic CJD, some evidence suggests earlier age of onset in genetic CJD (60 years) than in sporadic CJD (65 years).

**Iatrogenic CJD** has been recognized after exposure of nervous-tissue-contaminated surgical instruments and in dura mater or human growth hormone extracted from cadaveric pituitary glands.

**Variant CJD.** Following the bovine spongiform encephalopathy (BSE) epidemic in the UK and elsewhere in the 1990s, variant CJD was identified as the only human prion disease with a confirmed zoonotic origin. The clinical syndrome is characterized by early disease onset (frequently before age 30 years) with psychiatric manifestations and prominent paresthesias that are followed by cognitive decline, ataxia, muscle stiffness, myoclonus, and akinetic mutism. In contrast to sporadic CJD, in variant CJD abnormal prion protein deposits are present in the tonsils and appendix. Brain imaging reveals typical high signal intensities in the posterior thalamus ("hockey stick sign") [Zeidler et al 1997].

# Management

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with genetic prion disease, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Because of very rapid disease progression and short survival time after the diagnosis, evaluations for supportive care must be performed early. They include the following:

- Need for gastrostomy tube feeding for nutrition and to reduce risk of aspiration
- Evaluation for bladder and bowel incontinence
- Need for physical therapy and occupational therapy for mobility and activities of daily living

- Psychiatric manifestations
- Consultation with a social worker (or other medical professional) to determine need for:
  - Caregiver support including use of community resources & support/advocacy organizations
  - Specific 24-hour/day care assistance
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of genetic prion disease in order to facilitate medical and personal decision making

## Treatment of Manifestations

No treatment of the underlying cause of genetic prion disease is available. Only a few controlled trials have been performed. Some data point toward slowing of disease progression with doxycycline (100-200 mg/day) when administered early in the disease course [Varges et al 2017].

Supportive care by a multidisciplinary team of specialists including neurologists, psychiatrists, physical therapists, occupational therapists, speech and language therapists, and social workers is recommended.

Symptomatic treatment may include the following:

- For psychiatric manifestations such as depression or psychosis, antidepressant or neuroleptic treatment
- Myoclonic jerks respond well to clonazepam.
- Muscle rigidity may require dopamine or dopaminergic drugs.
- Spasticity may respond to regular antispastic medication.
- Physical therapy for exercises and/or stretching to prevent contractures; durable medical devices for positioning and/or mobility
- Occupational therapy for home adaptation to improve safety and activities of daily living
- Feeding issues addressed by nutritionists, speech pathologists
- Communication (including alternative means of communication) by speech pathologists

## Surveillance

Because of very rapid disease progression, close periodic monitoring by the multidisciplinary team is needed, typically every 14 days to evaluate need for treatment of symptoms.

## Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

# Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

## Mode of Inheritance

Genetic prion disease is inherited in an autosomal dominant manner.

## Risk to Family Members

**Parents of a proband.** Of note, family history of a neurodegenerative disease may be suggestive in a proportion of affected individuals only and the rate of positive family history varies across pathogenic variants and between countries. Probably the most information is available from affected individuals with the E200K or V210I variant. Clusters of affected individuals with E200K variants have been identified from Chile, Israel, Slovakia, Argentina, Australia, Japan, and China. While a positive family history has been reported in all affected individuals from Chile and Israel, in other countries the incidence of a positive family history varies between 44% and 60%. For the V210I variant, a positive family history varies between 12% and 21% [Ladogana & Kovacs 2018].

- Some individuals diagnosed with genetic prion disease have a parent who is heterozygous for a *PRNP* pathogenic variant. Because *PRNP* pathogenic variants may be associated with reduced penetrance, a parent who is heterozygous for a *PRNP* pathogenic variant may or may not have manifestations of genetic prion disease.
- Some individuals with genetic prion disease have the disorder as the result of a *de novo PRNP* pathogenic variant. The proportion of individuals with genetic prion disease caused by a *de novo* pathogenic variant is unknown.
- Molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Though theoretically possible, no instances of a proband inheriting a *PRNP* pathogenic variant from a parent with germline mosaicism have been reported. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism.
- The family history of some individuals diagnosed with genetic prion disease may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, or early death of the parent before the onset of symptoms. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband [Synofzik et al 2009].

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have a pathogenic *PRNP* variant, the risk to sibs is 50%.
  - The likelihood that a heterozygous sib will develop manifestations of genetic prion disease varies depending on the specific *PRNP* pathogenic variant segregating in the family. Some *PRNP* pathogenic variants (e.g., E200K) are considered highly penetrant whereas other variants (e.g., V210I) are associated with a penetrance as low as approximately 10% [Kim et al 2018].
  - A sib who inherits a familial *PRNP* pathogenic variant may have a clinicopathologic phenotype that is distinct from that of the proband [Synofzik et al 2009, Ladogana & Kovacs 2018].

- If the proband has a known *PRNP* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *PRNP* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for genetic prion disease because of the possibility of age-related penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

**Offspring of a proband.** Each child of an individual with a pathogenic variant in *PRNP* has a 50% chance of inheriting the variant.

**Other family members.** The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected or has a *PRNP* pathogenic variant, the parent's family members are at risk.

## Related Genetic Counseling Issues

**Predictive testing** (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *PRNP* pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

**Predictive testing in minors** (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of genetic prion disease, it is appropriate to consider testing of symptomatic individuals regardless of age.

**Family planning**

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are at risk.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *PRNP* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for genetic prion disease are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion

of these issues may be helpful. For more information, see the National Society of Genetic Counselors position statement on prenatal testing in adult-onset conditions.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **CJD International Support Alliance (CJDISA)**
  www.cjdisa.com
- **Creutzfeldt-Jakob Disease Foundation, Inc.**
  341 West 38th Street
  Suite 501
  New York City NY 10018
  **Phone:** 800-659-1991; 212-719-5900
  www.cjdfoundation.org
- **MedlinePlus**
  Prion disease

## Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** Genetic Prion Disease: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *PRNP* | 20p13 | Major prion protein | PRNP database<br>Prion Protein/CJD database | PRNP | PRNP |

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

**Table B.** OMIM Entries for Genetic Prion Disease (View All in OMIM)

| | |
|---|---|
| 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 |

## Molecular Pathogenesis

*PRNP* encodes the major prion protein, a glycoprotein (PrPC) that is attached to the plasma membrane. The normal function of PrPC is unknown, although roles in synapse formation, delivery of copper to cells, and cell signaling have been proposed.

**Mechanism of disease causation.** A *PRNP* pathogenic variant changes the non-pathogenic (cellular) prion protein (PrPC) to a pathogenic (scrapie-inducing) protein (PrPSc) that is abnormal and misfolded [Prusiner 1998]. The effect of a pathogenic variant is presumed to be destabilization of prion protein, which enhances the propensity for the protein to attain the PrPSc state. PrPSc then behaves as a conformational template, which complexes with non-pathogenic PrPC. The manner in which the accumulation of PrPSc is toxic to the cell is unknown.

***PRNP*-specific laboratory technical considerations.** The first exon of *PRNP* is noncoding; the prion protein is encoded by a single exon typically designated as exon 2 (NM_000311.3).

The designation of the polymorphic variant at nucleotide 385 will vary depending on the reference sequence used. The *PRNP* reference sequence NM_000311.3 has an A at the polymorphic nucleotide 385 (c.385A), thereby encoding M129 (p.Met129). Other *PRNP* reference sequences may have the polymorphic nucleotide c.385G and encode V129 (p.Val129). See rs1799990.

Insertional pathogenic variants are associated with the genetic Creutzfeldt-Jakob disease phenotype and the Gerstmann-Sträussler-Scheinker syndrome phenotype. Insertion variants of one or more octapeptide repeat segments (sometimes designated as a duplication) predict a prion protein extended by additional amino acids. The insertion variants involve one or more additional octapeptide repeat segments between codons 51 and 90, a highly unstable region that is enriched for encoding proline, glycine, and glutamine residues. Each repeat segment adds 24 nucleotides (i.e., 8 amino acids). Typically, these variants are described as an octapeptide repeat rather than a 24-bp nucleotide repeat because the nucleotide sequence encoding the octapeptide varies.

Normal *PRNP* alleles have one nonapeptide followed by four octapeptide tandem repeat sequences, each of which comprises the following amino acids: Pro-(His/Gln)-Gly-Gly-Gly-(-/Trp)-Gly-Gln. An additional 1-12 repeats has resulted in significant clinical and neuropathologic phenotypes of genetic prion disease [Ladogana & Kovacs 2018].

**Table 4.** Notable *PRNP* Variants

| Reference Sequences | Predicted Protein Change | DNA Nucleotide Change | Comment [Reference] |
|---|---|---|---|
| NM_000311.3<br>NP_000302 | E200K (p.Glu200Lys) | c.598G>A | Assoc w/gCJD phenotype. See footnote 1 [Ladogana & Kovacs 2018]. |
| | V210I (p.Val210Ile) | c.628G>A | Assoc w/gCJD phenotype. See footnote 1 [Ladogana & Kovacs 2018]. |
| | P102L (p.Pro102Leu) | c.305C>T | Assoc w/GSS syndrome phenotype. See footnote 1 [Ladogana & Kovacs 2018]. |
| | V180I (p.Val180Ile) | c.538G>A | See footnote 1 [Ladogana & Kovacs 2018]. |
| | D178N (p.Asp178Asn) | c.532G>A | Assoc w/FFI phenotype [Ladogana & Kovacs 2018]; 1 of the 5 most common variants that account for 85% of gPrD when *in cis* w/M129 (p.[Asp178Asn;Met129Val]) [2, 3] |

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
FFI = fatal familial insomnia; gCJD = genetic Creutzfeldt-Jakob disease; gPrD = genetic prion disease; GSS = Gerstmann-Sträussler-Scheinker
*1.* One of the five most common variants that account for 85% of gPrD [Ladogana & Kovacs 2018]
*2.* Note that p.[Asp178Asn;Met129Val] is the HGVS standard nomenclature for two variants on one allele (i.e., on one chromosome; *in cis*), commonly referred to as a haplotype. p.Met129Val indicates that the Met residue at codon 129 in this reference sequence changes to a Val.
*3.* The phenotype in persons w/the p.Asp178Asn pathogenic variant typically depends on which variant – Val129 or Met129 – is in *cis* configuration (see Genotype-Phenotype Correlations).

# Chapter Notes

## Author Notes

www.demenzzentrum-goettingen.de

## Acknowledgments

This research was funded by the Robert Koch-Institute through funds of the Federal Ministry of Health (grant no 1369-341), cjd-goettingen.de.

## Author History

James A Mastrianni, MD, PhD; University of Chicago (2003-2020)
Matthias Schmitz, MD (2021-present)
Inga Zerr, MD (2021-present)

## Revision History

- 7 January 2021 (bp) Comprehensive update posted live
- 2 January 2014 (me) Comprehensive update posted live
- 7 September 2010 (cd) Revision: prenatal testing available clinically
- 18 December 2008 (me) Comprehensive update posted live
- 7 October 2005 (cd) Revision: targeted mutation analysis for common mutations no longer clinically available

- 16 May 2005 (me) Comprehensive update posted live
- 4 March 2004 (cd) Revisions: Testing
- 27 March 2003 (me) Review posted live
- 12 April 2002 (jm) Original submission

# References

## Published Guidelines / Consensus Statements

Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 1-9-24.

National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2018. Accessed 1-9-24.

## Literature Cited

Cracco L, Appleby BS, Gambetti P. Fatal familial insomnia and sporadic fatal insomnia. Handb Clin Neurol. 2018;153:271-99. PubMed PMID: 29887141.

D'Alessandro M, Petraroli R, Ladogana A, Pocchiari M. High incidence of Creutzfeldt-Jakob disease in rural Calabria, Italy. Lancet. 1998;352:1989-90. PubMed PMID: 9872257.

Geschwind MD. Rapidly progressive dementia. Continuum (Minneap Minn). 2016;22:510-37. PubMed PMID: 27042906.

Kim MO, Takada LT, Wong K, Forner SA, Geschwind MD. Genetic PrP prion diseases. Cold Spring Harb Perspect Biol. 2018;10:a033134. PubMed PMID: 28778873.

Krasnianski A, Heinemann U, Ponto C, Kortt J, Kallenberg K, Varges D, Schulz-Schaeffer WJ, Kretzschmar HA, Zerr I. Clinical findings and diagnosis in genetic prion diseases in Germany. Eur J Epidemiol. 2016;31:187-96. PubMed PMID: 26076917.

Ladogana A, Kovacs GG. Genetic Creutzfeldt-Jakob disease. Handb Clin Neurol. 2018;153:219-42. PubMed PMID: 29887139.

Lee HS, Sambuughin N, Cervenakova L, Chapman J, Pocchiari M, Litvak S, Qi HY, Budka H, del Ser T, Furukawa H, Brown P, Gajdusek DC, Long JC, Korczyn AD, Goldfarb LG. Ancestral origins and worldwide distribution of the PRNP 200K mutation causing familial Creutzfeldt-Jakob disease. Am J Hum Genet. 1999;64:1063-70. PubMed PMID: 10090891.

Mitrová E, Belay G. Creutzfeldt-Jakob disease with E200K mutation in Slovakia: characterization and development. Acta Virol. 2002;46:31-9. PubMed PMID: 12197632.

Prusiner SB. Prions. Proc Natl Acad Sci U S A. 1998;95:13363-83. PubMed PMID: 9811807.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126-33. PubMed PMID: 26656846.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Schmitz M, Dittmar K, Llorens F, Gelpi E, Ferrer I, Schulz-Schaeffer WJ, Zerr I. Hereditary human prion diseases: an update. Mol Neurobiol. 2017;54:4138-49. PubMed PMID: 27324792.

Spudich S, Mastrianni JA, Wrensch M, Gabizon R, Meiner Z, Kahana I, Rosenmann H, Kahana E, Prusiner SB. Complete penetrance of Creutzfeldt-Jakob disease in Libyan Jews carrying the E200K mutation in the prion protein gene. Mol Med. 1995;1:607-13 PubMed PMID: 8529127.

Synofzik M, Bauer P, Schöls L. Prion mutation D178N with highly variable disease onset and phenotype. J Neurol Neurosurg Psychiatry. 2009;80:345-6. PubMed PMID: 19228673.

Takada LT, Kim MO, Cleveland RW, Wong K, Forner SA, Gala II, Fong JC, Geschwind MD. Genetic prion disease: experience of a rapidly progressive dementia center in the United States and a review of the literature. Am J Med Genet B Neuropsychiatr Genet. 2017;174:36-69. PubMed PMID: 27943639.

Tesar A, Matej R, Kukal J, Johanidesova S, Rektorova I, Vyhnalek M, Keller J, Eliasova I, Parobkova E, Smetakova M, Musova Z, Rusina R. Clinical variability in P102L Gerstmann-Sträussler-Scheinker syndrome. Ann Neurol. 2019;86:643-52. PubMed PMID: 31397917.

Varges D, Manthey H, Heinemann U, Ponto C, Schmitz M, Schulz-Schaeffer WJ, Krasnianski A, Breithaupt M, Fincke F, Kramer K, Friede T, Zerr I. Doxycycline in early CJD: a double-blinded randomised phase II and observational study. J Neurol Neurosurg Psychiatry. 2017;88:119-25. PubMed PMID: 27807198.

Zeidler M, Stewart GE, Barraclough CR, Bateman DE, Bates D, Burn DJ, Colchester AC, Durward W, Fletcher NA, Hawkins SA, Mackenzie JM, Will RG. New variant Creutzfeldt-Jakob disease: neurological features and diagnostic tests. Lancet. 1997;350:903-7. PubMed PMID: 9314867.

## License