GENEReviews

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Prion Diseases

[*Transmissible Spongiform Encephalopathies (TSEs). Includes: Familial Creutzfeldt-Jakob Disease (fCJD), Gerstmann-Sträussler-Scheinker Disease (GSS), Fatal Familial Insomnia (FFI)*]

James A Mastrianni, MD, PhD
Assistant Professor, Department of Neurology
Co-Director, Center for Comprehensive Care and Research on Memory Disorders
Committees of Neurobiology and Microbiology
University of Chicago
jmast@neurology.bsd.uchicago.edu

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Summary

Disease characteristics. Genetically transmissible human prion diseases manifest, in general, 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. Three phenotypes classically associated with genetically transmissible prion disease, familial Creutzfeldt-Jakob disease (fCJD), Gerstmann-Sträussler-Scheinker (GSS) syndrome, and fatal familial insomnia (FFI), were defined by clinical and neuropathologic findings long before the molecular basis of prion disease was discovered. Although it is now recognized that these three phenotypes are part of a continuum and have overlapping features, recognition of these phenotypes can be useful when providing affected individuals and families with information about the expected clinical course. The age at onset ranges from the third to ninth decade of life. The course ranges from a few months to several years (typically, five to seven years; in rare cases, more than ten years). Death generally results from infection, either by pneumonia (typically from aspiration) or urosepsis.

Diagnosis/testing. *PRNP* is the only gene known to be associated with genetically transmissible human prion disease. The presence of a *PRNP* mutation is necessary to establish the diagnosis of genetically transmissible human prion disease in a symptomatic individual. Sequence analysis of the *PRNP* open reading frame is available on a clinical basis. It is possible that this analysis does not detect all disease-causing mutations; thus, the absence of a *PRNP* disease-causing mutation does not rule out the diagnosis of genetically transmissible human prion disease.

Genetic counseling. Genetically transmissible human prion disease is inherited in an autosomal dominant manner. Most individuals diagnosed with genetically transmissible human prion disease have an affected parent. However, a proband with genetically transmissible human prion disease may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* gene mutations is unknown. Each child of an individual with a disease-causing *PRNP* mutation has a 50% chance of inheriting the mutation. Prenatal testing may be available through laboratories offering custom prenatal testing.

Diagnosis

Clinical Diagnosis

Before it was discovered that genetically transmissible human prion disease (genetic prion disease) could be attributed to mutations in a single gene, three phenotypes, labeled familial Creutzfeldt-Jakob disease (fCJD), Gerstmann-Sträussler-Scheinker (GSS) syndrome, and fatal familial insomnia (FFI), were recognized clinically and neuropathologically. It is now known that these phenotypes are not distinct entities but rather constitute a continuum of clinical manifestations of prion disease; nonetheless, certain aspects of these phenotypes are useful in 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, including: dementia, psychiatric symptoms, dyscoordination of movements (ataxia, dysarthria), weakness and/or spasticity, strokelike episodes, seizures, and autonomic disturbance
- Neuropathologic findings that include spongiform change and astrogliosis diffusely distributed throughout the cortex and deep nuclei of the brain (fCJD); multiple amyloid plaques to which anti-PrP antibodies bind (GSS); a relative lack of spongiform change and presence of neuronal dropout and gliosis primarily within the thalamus and inferior olivary nucleus of the brainstem (FFI) [DeArmond & Prusiner 1997]
- A family history consistent with autosomal dominant inheritance
- Identification of a disease-causing mutation of the *PRNP* gene

Other studies, such as electroencephalogram (EEG), brain imaging, or examination of cerebrospinal fluid (CSF) may be helpful in supporting the diagnosis, but none is diagnostic on its own. Often these studies are performed to evaluate for other potentially treatable diseases of the central nervous system (see Differential Diagnosis.) It should be emphasized that these tests have been best studied and are most helpful in the diagnosis of non-genetic prion disease (i.e., sporadic CJD). Reliance, therefore, on these studies for the diagnosis of genetic prion disease is cautioned.

- **EEG.** Characteristic EEG findings of periodic sharp wave complexes (PSWCs), consisting of triphasic or sharp wave bursts every 0.5 to 2.0 seconds, can suggest the diagnosis of genetic prion disease. Although PSWCs are observed in a relatively small percentage of individuals with genetic prion disease, their presence appears 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 appear more likely to have a positive EEG. 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**
  - Magnetic resonance imaging (MRI) may show mild to moderate generalized atrophy at the time of presentation or within a short interval after presentation.
  - T_2-weighted images may demonstrate hyperintensity of the basal ganglia. Diffusion-weighted MRI (DWI) appears to be more sensitive and specific in this regard. In some reports, increased signal appears within the cortical ribbon before it appears in the deeper structures in sCJD. A small number of reports suggest similar findings in genetic prion disease.

- PET or SPECT scanning, with the exception of FFI, appears to be of limited usefulness in diagnosing genetic prion disease, as the findings show nonspecific and diffuse cortical hypometabolic activity, sometimes with frontal predominance. In some reports, a reduction in perfusion to specific brain regions correlates with the clinical symptoms observed in the individual (e.g., left frontal or occipital cortex affected in language or visual deficits, respectively). In the FFI phenotype the PET scan demonstrates a significant and selective reduction in activity within the thalamus, often early in the disease.

- **CSF (cerebrospinal fluid).** An elevation of CSF protein concentration by approximately 10% is common, and may be attributed, at least in part, to release of the normal neuronal protein 14-3-3 into the CSF following neuronal death; however, this is a nonspecific finding. Because a significant number of neurons die in individuals with prion disease, the concentration of the 14-3-3 protein in CSF may increase substantially in some but not all cases. Because of the generally slower rate of progression of genetic prion disease, the detection of the 14-3-3 protein in the CSF of these individuals appears less consistent than with sporadic CJD. It is also important to note that the 14-3-3 protein is released into the CSF in herpes encephalitis and hypoxic brain damage resulting from stroke, Hashimoto's encephalopathy, Alzheimer disease, and, on occasion, multiple sclerosis [Zerr et al 1998, Satoh et al 1999, Huang et al 2003]. More recently, Van Everbroeck et al (2005) reported a more specific antibody to the gamma isoform of 14-3-3 that is more reliable against false positive tests.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *PRNP* is the only gene known to be associated with genetically transmissible human prion disease.

The presence of a *PRNP* mutation is necessary to establish the diagnosis of genetically transmissible prion disease in a symptomatic individual.

Molecular genetic testing: Clinical uses

- Diagnostic testing
- Predictive testing

Molecular genetic testing: Clinical method

- **Sequence analysis.** Sequence analysis of the *PRNP* open reading frame is available on a clinical basis.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in the Diagnosis of Genetically Transmissible Prion Diseases

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis	*PRNP* sequence alterations	Unknown [1]	Clinical Testing

1. By definition, "genetically transmissible" prion disease requires the presence of a disease-causing *PRNP* mutation; however, it is possible that sequence analysis does not detect all disease-causing mutations. Thus, the absence of a disease-causing mutation does not rule out the diagnosis.

Interpretation of test results

- Because identification of a *PRNP* mutation is required to make the diagnosis of a genetically transmissible human prion disease, it is important to consider possible outcomes of sequence analysis.
- For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related Disorders

No other phenotypes are known to be associated with mutations in *PRNP*. Although a single report suggested that the N171S polymorphism in *PRNP* was associated with schizophrenia [Samaia et al 1997], the mutation had been previously reported in a normal individual, and in addition, it was not present in all members of the reported family with schizophrenia.

A single case of a diffuse Lewy body disease phenotype associated with the *PRNP* mutation M232R has been reported. Whether the mutation and the phenotype are causally related remains uncertain [Koide et al 2002].

Clinical Description

Natural History

Prion diseases generally manifest with cognitive difficulties, ataxia, and myoclonus (abrupt jerking movements of muscle groups and/or entire limbs); however, the order and/or predominance of these features and associated neurologic and psychiatric findings vary with prion disease subtype and/or *PRNP* mutation. The age at onset ranges from the third to ninth decade of life. The course ranges from a few months to several years (typically five to seven years, but in rare cases more than ten years). Death generally results from infection, either by pneumonia (typically from aspiration) or urosepsis.

The three phenotypes classically associated with genetic prion disease (fCJD, GSS, and FFI), were defined by clinical and neuropathologic findings long before the molecular basis of this group of disorders was discovered. Although it is now recognized that these three phenotypes are part of a continuum and have overlapping features, it can be helpful to think of genetic human prion disease at least in part in terms of these phenotypes when providing individuals and families with information about the expected clinical course. Detailed phenotype/genotype correlations of these various syndromes can be found in Mastianni 1998, Gambetti et al 1999, and Kovacs et al 2002.

Familial Creutzfeldt-Jakob disease (fCJD). Progressive confusion and memory impairment occur first, followed by ataxia and myoclonus. The disease typically manifests between the ages of 30 and 50 years, although a few individuals present before age 30 or as late as the upper 80s. The course from onset to death ranges from a few months to five years. At the endstage of disease, the individual is generally bedbound, mute, and immobile, except for myoclonic jerks.

The cognitive impairment observed may initially be mild confusion or it may be specific for a particular cortical function, such as language or constructional abilities; however, the resultant picture is one of global dementia. As the disease progresses, neurobehavioral symptoms may vary considerably. Psychiatric features, including delusions and hallucinations, may also occur.

Ataxia may be either truncal or appendicular, manifesting either as an unsteady gait, clumsiness while carrying out commonly performed tasks (e.g., picking up the salt shaker while dining), or progressive dysarthria. As the ataxia progresses, the individual may fall repeatedly, necessitating the use of a wheelchair to prevent injury.

Myoclonus generally, but not always, occurs after cognitive impairment is evident. Myoclonus 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 have been observed.

Gerstmann-Sträussler-Scheinker syndrome (GSS). GSS typically begins in the fourth to sixth decade with the insidious onset of cerebellar dysfunction, manifest as unsteady gait and mild dysarthria [Ghetti et al 1996]. Cognitive dysfunction is generally not apparent early on; however, with progression, bradyphrenia, or slowness of thought processing, may become evident. Pyramidal involvement with spasticity and/or extrapyramidal involvement with bradykinesia, increased muscle tone with or without cogwheeling, and masked facies are also common. Psychiatric or behavioral symptoms are atypical. The disease progresses at a relatively slow but relentless pace over the course of a few to seven or more years. Cerebellar dysfunction results in severe dysarthria, gait and appendicular ataxia, ocular dysmetria, and lack of coordination in swallowing. A decline in cognitive abilities, particularly of concentration and focus, becomes apparent with progression into the late stage of disease. In the terminal stage, the individual is bedridden from the disabling ataxia, unable to eat because of severe lack of coordination in swallowing, and unable to communicate because of the profound dysarthria; yet insight into his/her condition may remain. This pattern of progression relates to the cerebellar nature of this disease, with progression into the brain stem and eventually the cerebrum.

Fatal familial insomnia (FFI). FFI typically presents in midlife (40s to 50s) with the insidious or subacute onset of insomnia, initially manifest as a mild, then more severe, reduction in overall sleep time [Gambetti et al 1995]. When sleep is achieved, vivid dreams are common. A disturbance in autonomic function then emerges, which may manifest as elevated blood pressure, episodic hyperventilation, excessive lacrimation, sexual and urinary tract dysfunction, and/or a change in basal body temperature. Signs of brainstem involvement, such as decreased ability to gaze upward, double vision, jerky eye pursuit movements, or dysarthric speech may also appear in some individuals. With continued progression over the next few months, individuals develop truncal and/or appendicular ataxia. The speed of thought processing may be reduced, as is common in subcortical dementing states, and memory impairment may be variable; however, compared with other more prominent features of disease, cognitive capacity is relatively spared until late in the course. Advancing 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 the most common immediate cause of death. The typical duration of disease is 12 to 16 months, with a range of a few months to five years.

Neuropathology. The various prion disease syndromes have relatively characteristic neuropathologic changes such as abundant deposition of amyloid plaques that stain positive with PrP antibodies in GSS, focal thalamic neuronal loss and gliosis in FFI, and diffusely distributed spongiform change with neuronal destruction in fCJD. Although characteristic of

each syndrome, the neuropathology is not 100% specific and variations from case to case are apparent [Gambetti et al 1999, Kovacs et al 2002].

Genotype-Phenotype Correlations

Several point mutations of *PRNP* cause the fCJD phenotype (D178N with V129, V180I, T183A, E200K, R208H, V210I, M232R) and GSS phenotype (P102L, P105L, A117V, Y145Stop, Q160Stop, F198S, and Q217R). Only one point mutation causes FFI (D178N with M129).

Insertional mutations are associated with either the fCJD phenotype or GSS phenotype. These insertions all lie within a region of *PRNP* that includes a string of eight amino acids rich in proline, glycine, and glutamine that is repeated five times. From one to nine additional repeat segments have been detected in familial forms of prion disease. A correlation seems to exist such that from two to seven repeats are typically associated with a fCJD phenotype, while eight or nine repeats have been found in association with a GSS phenotype. Of note, some of the families with such repeats show significant phenotypic variability among affected individuals.

Codon 129: A common polymorphism exists at codon 129 of *PRNP* that codes for either the amino acid methionine (Met) or valine (Val). Approximately 50% of the Caucasian population is homozygous at this polymorphic site for either Met or Val, although 80-90% of individuals with sporadic CJD are homozygotes [Owen et al 1990].

- The onset of genetically transmissible prion disease is generally earlier and its course shorter in individuals homozygous at codon 129 compared with those heterozygous at codon 129.
- The Met/Val polymorphism modifies the phenotype of disease, most notably in cis configuration with the D178N mutation.
  - If Val is encoded, the phenotype is typical CJD.
  - If Met is encoded, the phenotype is FFI.
  - Even in nonfamilial forms of CJD, this polymorphism appears to have an effect on disease phenotype such that individuals with Met homozygosity present most often with dementia and a more rapid course, whereas those with a Val on one or both alleles display ataxia at onset and a slower progression of disease [Parchi, Giese et al 1999].

Penetrance

The E200K and V210I mutations of *PRNP* are commonly associated with a variable, but generally age-dependent penetrance, such that the older the individual, the greater likelihood of his/her manifesting the disease. Because of this, it is not uncommon to encounter a situation in which the parent of an affected individual may be unaffected but has a *PRNP* mutation.

Most other *PRNP* mutations demonstrate complete penetrance.

Prevalence

Prion diseases are rare. The general worldwide yearly incidence is approximately one case per million people. Thus, in the US, approximately 300 *de novo* cases of sporadic and genetic prion disease are observed per year. The genetically transmissible forms of prion disease are about one-tenth as common as the sporadic forms. This prevalence is comparable to that observed with the autosomal dominant forms of familial Alzheimer disease and amyotrophic lateral sclerosis (Lou Gehrig's disease).

The most common disease-associated mutations of *PRNP* are the E200K, the largest focus being present in the Middle East (Lyban Jews) and western Europe (Slovakia), and the D178N mutation, which is found worldwide. Other mutations are relatively rare.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Other prion diseases. About 10-15% of prion diseases are genetically transmissible, while the remainder occur from unknown risk factors or are acquired through infection with prions; these include sporadic Creutzfeldt-Jakob disease (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.

- **sCJD.** The clinical and pathologic features of sCJD are the same as fCJD; however, the duration of disease is typically much shorter, on the average of six months or less, and the age at onset is later, typically after age 60 years.
- **sFI.** The phenotype is the same as in FFI, including age at onset and duration of disease [Mastrianni et al 1999; Parchi, Capellari et al 1999]. sFI is much less common than FFI.
- **iCJD.** Diagnosis of this form of prion disease requires the identification or strong association with administration of a biological extract or tissue contaminated with prions. Such sources have included injections of human growth hormone contaminated with prions (used prior to 1980), improperly decontaminated depth electrodes previously used in individuals with CJD, transplantation of corneas obtained from individuals with CJD, dura mater grafts contaminated with prions, and various poorly documented neurosurgical procedures [Mastrianni & Roos 2000].
- **vCJD.** This prion disease represents a relatively new strain of CJD acquired by ingestion of beef or beef products contaminated with bovine spongiform encephalopathy (BSE), the prion disease of cattle (commonly known as mad cow disease). The typical clinical picture is that of a young adult or teen who develops behavioral changes and/or pain in the lower extremities that eventually lead to a progressive dementia with ataxia and myoclonus [Will et al 2000]. The course is about 1.5 years. The EEG is often diffusively slow rather than periodic, and the 14-3-3 CSF protein test is more often negative than positive. Neuropathology reveals spongiform change spread diffusely throughout the brain and dense amyloid plaque deposition surrounded by a halo of vacuolation described as "florid plaques" [Ironside 1998].

Other. Prion disease should always be considered a possible diagnosis in an individual with a progressive cognitive decline, either in isolation or when combined with a movement disorder. The rapidity of progression may be a helpful clue; however, some prion diseases, especially genetically-based ones, may progress slowly. Genetically transmissible human prion diseases may be easily confused with several other neurodegenerative diseases such as Alzheimer disease, dementia with Lewy bodies, Huntington disease, progressive supranuclear palsy, the inherited ataxias, and the frontotemporal dementias, including progressive subcortical gliosis, dementia with motor neuron disease, Pick disease, and FTD with parkinsonism (chromosome 17-linked FTD).

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

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

A typical evaluation includes a physical examination, with focus on the neurologic features of cognition, motor function, and coordination.

Treatment of Manifestations

Therapy is aimed at controlling symptoms that may cause discomfort.

- If present, seizures may be treated with general anti-epileptic drugs (AEDs) such as diphenylhydantoin or carbamazepine.
- Myoclonus can sometimes be mitigated by clonazepam.
- Issues related to dysphagia are often difficult to resolve. Since the disease is terminal, families are often faced with the difficult decision of whether or not to place a permanent feeding tube. The timing of this decision differs depending on the type of prion disease.

The affected individual does NOT need to be quarantined. While all prion diseases are transmissible through ingestion or injection of infectious tissue (neural), they are not contagious by typical means of close contact with affected individuals. It is advisable, however, that body fluids be handled as biohazard waste.

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

Prevention of Primary Manifestations

No cure for prion disease currently exists.

Surveillance

Affected individuals are routinely examined at regular intervals for complications related to swallowing difficulties, infections, etc.

Therapies Under Investigation

A clinical trial is currently underway in the US and the UK to test quinacrine, an antimalarial agent that showed promise in tissue culture, but results in rodents have not been promising.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Genetically transmissible human prion disease is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with genetically transmissible human prion disease have an affected parent. However, a proband with a genetically transmissible human prion disease may have the disorder as the result of a *de novo* gene mutation.
- The proportion of cases caused by *de novo* gene mutations is unknown.
- In addition, families in which penetrance appears to be reduced have been observed; thus the parent with a disease-causing mutation is unaffected while the child is affected.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected or has a disease-causing *PRNP* mutation, the risk to the sibs of inheriting the allele is 50%.
- If the parents are clinically unaffected and do not have a *PRNP* disease-causing mutation, the risk to the sibs of a proband appears to be low.
- If a *PRNP* mutation cannot be detected in the DNA of either parent, it is presumed that the proband has a *de novo* gene mutation and the risk to the sibs of the proband depends on the spontaneous mutation rate of *PRNP* and the probability of germline mosaicism. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with a disease-causing *PRNP* mutation has a 50% chance of inheriting the mutation.

Other family members

- The risk to other family members depends upon the status of the proband's parents.
- If a parent is found to be affected or to have a disease-causing *PRNP* mutation, his or her family members are at risk.

Related Genetic Counseling Issues

Molecular genetic testing of symptomatic individuals from families without family histories of neurological disease. Goldman et al (2004) stress the importance of pretest counseling for families of symptomatic individuals with no family history of neurological disease to better prepare families and to allow them to make informed decisions about receiving genetic test results.

Testing of at-risk asymptomatic adults. Testing of at-risk asymptomatic adults for genetically transmissible human prion diseases is available using the same techniques described in Molecular Genetic Testing. This testing 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 genetically transmissible prion diseases, an affected family member must be tested first to confirm that the disorder in the family is actually one of the genetically transmissible prion diseases.

Testing for the disease-causing mutation in the absence of definite symptoms of the disease is predictive testing. At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. Others

may have different motivations including simply the "need to know." Testing of asymptomatic at-risk adult family members usually involves pre-test interviews in which the motives for requesting the test, the individual's knowledge of genetically transmissible prion diseases, the possible impact of positive and negative test results, and neurologic status are assessed. 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. 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 of age 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 [Bloch & Hayden 1990, Harper & Clarke 1990]. In addition, no preventive treatment for prion diseases is available.

(See also the National Society of Genetic Counselors resolution on genetic testing of children and the American Society of Human Genetics and American College of Medical Genetics points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents.)

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA, particularly in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of genetically transmissible human prion diseases are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. For laboratories offering custom prenatal testing, see Testing.

Requests for prenatal testing for late-onset conditions such as genetically transmissible human prion diseases are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination. Although most centers would

consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD). Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Prion Diseases

Gene Symbol	Chromosomal Locus	Protein Name
PRNP	20pter-p12	Major Prion Protein (PrP)

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Prion Diseases

123400	CREUTZFELDT-JAKOB DISEASE; CJD
137440	GERSTMANN-STRAUSSLER DISEASE; GSD
176640	PRION PROTEIN; PRNP
245300	KURU, SUSCEPTIBILITY TO
600072	FAMILIAL FATAL INSOMNIA; FFI

Table C. Genomic Databases for Prion Diseases

Gene Symbol	Locus Specific	Entrez Gene	HGMD
PRNP	PRNP	5621 (MIM No. 176640)	PRNP

For a description of the genomic databases listed, click here.

Normal allelic variants: The normal *PRNP* has a coding region of 756 nucleotides [Puckett et al 1991]. Several allelic variants have been detected that are not associated with an enhanced susceptibility to prion disease; however, these variants may play a role in altering the phenotype of disease from either sporadic or genetic forms of prion disease. These variants include the coding for valine at position 129 instead of methionine (M129V), glutamate instead of lysine at 219 (E219K), serine instead of asparagine at 171 (N171S), and a deletion of a single octarepeat segment. While these variants do not appear, in and of themselves, to promote disease, homozygosity at 129 appears to increase disease susceptibility, and depending on the substitution, this polymorphic site appears to affect the phenotype of disease. The E-to-K change at codon 219 has been reported as protective, although this change appears exclusive to the Japanese population.

Pathologic allelic variants: A host of pathologic allelic variants briefly mentioned in Genotype-Phenotype Correlations are known. Three major types of pathogenic mutations have been described:

- Nucleotide substitutions that result in an amino acid substitution. All of the mutations associated with pathology are in-frame heterozygous mutations with the exception of one report of an individual homozygous for the E200K mutation. The following amino acid substitutions have been reported: P102L, P105L, A117V, G131V, D178N,

V180I, T183A, T188K, T188R, H187R, F198S, E200K, R208H, V210I, Q217R, and M232R.

- A duplication of one or more octarepeat segments that result in an extended PrP. The insertion mutations involve the duplication of one or more octapeptide repeat segments between codons 51 and 90. Each repeat adds 24 nucleotides to the gene, or eight amino acids to the protein. From one to nine repeats have been associated with disease.
- The generation of an early stop signal that results in a truncated PrP. The substitutions that result in an early stop signal are Y145Stop and Q160Stop.

For more information, see Genomic Databases table above.

Normal gene product: The prion protein is translocated into the 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 anchor, by which the protein is attached to the cell surface. An octapeptide repeat segment is present between amino acids 51 and 90. Two asparagine-linked glycosylation sites are present. The normal function of the protein is unknown, although a role in synapse formation, the delivery of copper to cells, and a role in cell signaling, have been proposed. Two major isoforms of the prion protein exist: the non-pathogenic (cellular) form (PrP^{C}) and the pathogenic (scrapie-inducing) form (PrP^{Sc}) [Prusiner 1998]. 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% ß-pleated sheet; PrP^{C} is soluble in non-denaturing detergents, PrP^{Sc} is insoluble; PrP^{C} is completely degraded by proteases, PrP^{Sc} has a relative resistance to proteases.

Abnormal gene product: The normal protein product is presumably destabilized by the presence of a pathogenic mutation, which enhances the propensity for the protein to attain the PrP^{Sc} state. PrP^{Sc} then behaves as a conformational template that complexes with non-pathogenic PrP^{C}. The manner in which the accumulation of PrP^{Sc} is toxic to the cell is unknown.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Creutzfeldt-Jakob Disease Foundation, Inc
PO Box 5312
Akron, OH 44334
Phone: 800-659-1991; 330-665-5590
Fax: 330-668-2474
Email: crjakob@aol.com
http://www.cjdfoundation.org/

National Library of Medicine Genetics Home Reference
Prion disease

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

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Chapter Notes

Revision History

- 7 October 2005 (cd) Revision: targeted mutation analysis for common mutations no longer clinically available
- 16 May 2005 (me) Comprehensive update posted to live Web site
- 4 March 2004 (cd) Revisions: Testing
- 27 March 2003 (me) Review posted to live Web site
- 12 April 2002 (jm) Original submission