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REVIEW

Genetic counseling for prion disease: Updates and best practices

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ABSTRACT

Prion disease is a rare, fatal, and often rapidly progressive neurodegenerative disease. Ten to fifteen percent of cases are caused by autosomal dominant gain-of-function variants in the prion protein gene, *PRNP*. Rarity and phenotypic variability complicate diagnosis, often obscuring family history and leaving families unprepared for the genetic implications of an index case. Several recent developments inspire this update in best practices for prion disease genetic counseling. A new prion-detection assay has transformed symptomatic diagnosis. Meanwhile, penetrance, age of onset, and duration of illness have been systematically characterized across *PRNP* variants in a global cohort. Clinically, the traditional genotype–phenotype correlation has weakened over time, and the term genetic prion disease may now better serve providers than the historical subtypes Creutzfeldt-Jakob disease, fatal familial insomnia, and Gerstmann-Sträussler-Scheinker disease. Finally, in the age of genetically targeted therapies, clinical trials for prion disease are being envisaged, and healthy at-risk individuals may be best positioned to benefit. Such individuals need to be able to access clinical services for genetic counseling and testing. Thus, this update on the genetics of prion disease and best practices for genetic counseling for this disease aims to provide the information needed to expand genetic counseling services.

Introduction

Human prion disease is a rare, fatal neurodegenerative disease, major subtypes of which include Creutzfeldt-Jakob disease (CJD), fatal familial insomnia (FFI), and Gerstmann-Sträussler-Scheinker disease (GSS). Prion disease is the cause of roughly 1 in 6000 deaths,[1] with an incidence of 1 to 2 cases per million population per year.[2] Although 85% of cases are sporadic, with no known genetic or environmental trigger, approximately 10% to 15% are genetic, arising from autosomal dominant protein-altering variants in *PRNP*.[3] Acquired cases, made famous by the mad cow epidemic, are rare today. Regardless of etiology, prion disease is caused by the misfolding of the prion protein, which is termed PrP or PrP^{c} in its normal state. Misfolded PrP conformers, termed PrP^{Sc} or prions, act as templates for

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conformational conversion of additional PrP molecules.[4] Accumulation of prions in the brain gives rise to neurodegeneration with characteristic pathology; broad spongiform change is pathognomonic, whereas plaque and localized regional pathology are also seen in some cases. Although early symptoms vary widely, most cases rapidly advance into a progressive dementia with average duration of less than half a year.[5] Variability is seen in both presentation and duration of genetic prion disease cases and shows some association with *PRNP* genotype as further discussed in later sections. Diagnosis of prion disease is often delayed unless the patient is seen by a neurologist familiar with the disease.[6] Historical diagnostic tools have included selected magnetic resonance imaging, electroencephalogram, and nonspecific fluid biomarkers of neuronal damage.[7] Brain biopsy, formerly used in diagnosis, is presently discouraged. More recently, the disease-specific real-time quaking induced conversion assay, which detects prion seeds in cerebrospinal fluid or brain tissue, has revolutionized both pre- and postmortem diagnosis, offering >90% sensitivity and specificity, particularly for sporadic forms of prion disease.[8] The assay's reduced sensitivity to some genetic subtypes can be complemented by targeted sequencing of *PRNP*, which should be routinely offered for all suspected cases of prion disease, whether or not a family history is immediately apparent.[3]

In this article, we will consider the genetic forms of prion disease. More than half of these cases lack a documented family history and thus are more appropriately referred to as genetic than familial or hereditary.[9] Absent family history can be due to *de novo* pathogenic variants, incomplete penetrance, misattributed parenthood, adoption or estrangement, early death by other causes, or misdiagnosis of previous generations. Given the possibility of a genetic etiology, clinicians should consider offering genetic counseling and testing when diagnosing prion disease. Learning of genetic prion disease in the family can be shocking and terrifying, especially because of broader family implications. Families often struggle to find a provider knowledgeable about the disease and equipped to counsel about its genetic risk. This article will address issues pertinent to prion disease genetic counseling, including disease presentation, genetics, psychosocial counseling, and resources available to support patients, families, and those at risk.

Genetic Forms of Prion Disease

Genetic prion disease is caused by protein-altering variants in *PRNP* located on chromosome *20p13*. Of variants with strong evidence of pathogenicity, most are missense variants, but octapeptide repeat insertion (OPRI) variants and, in rare cases, truncating and frameshift variants can also cause disease.[3] Although many *PRNP* variants reported as pathogenic have subsequently been shown to convey modest or no risk, several variants cause disease with high penetrance, as shown by enrichment of these variants in prion disease cases over population controls and percentage of cases with positive family history.[10] The most common such highly penetrant variants are E200K, P102L, D178N, 6-OPRI, 5-OPRI, A117V, and P105L,[10] all of which meet American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) criteria PS4 (enrichment in cases over controls).[11] A total of 20 additional variants have been classified as likely highly penetrant on the basis of a combination of ACMG/AMP criteria PM2 (absence from controls in a large population data set) as well as either PS2 (*de novo* variant reported in a patient with no family history) or PP1 (cosegregation with disease in a pedigree with multiple affected); see Supplemental Table 1 for a full list. A handful of less penetrant variants, including V210I, V180I, and M232R, appear to convey 0.1% to 10% lifetime risk.[10]

In addition to these pathogenic variants, *PRNP* harbors 1 common sequence variant at codon 129, which can be occupied by either a methionine (M) or valine (V) residue. Codon 129 genotype influences duration of disease in some genetic prion disease, as well as risk in sporadic and iatrogenic prion disease.[3] This codon does not appear to influence age of onset for the most common genotypes in genetic prion disease,[12] although it may in rare cases.

The pathogenic variants listed earlier are associated with a spectrum of prion disease presentations. Some variants, including E200K, D178N-129V, and V210I, have historically been associated with the clinical term genetic CJD. The P102L, P105L and A117V variants were traditionally associated with GSS, whereas the D178N-129M variant was associated with FFI. The terms CJD, GSS, and FFI predate the discovery of *PRNP* as the single causal gene unifying all prion disease, and the field now recognizes abundant phenotypic heterogeneity within and overlap between these historical subtypes.[3,13,14] The current understanding of the most clinically relevant *PRNP* variants is described later in this article.

Classical phenotypes

Though most cases of prion disease converge toward progressive dementia, akinetic mutism, and ultimately, terminal illness, early symptoms vary widely in a manner not faithfully predicted by genotype. Diverse presentations have been reported not only within variants[15-21] but even within the same affected family[13,22,23] and between affected monozygotic twins.[24-26] However, despite its erosion over time, it is useful to be aware of the classical genotype–phenotype correlation (Table 1). First, although a simplified categorization can mislead in individual cases, some meaningful if imperfect group-wise distinctions persist, such as rapidly versus slowly progressive variants.[27] Second, patient and family awareness of classical subtypes may prime them to expect or notice certain symptoms. Educating families about the phenotypic spectrum may help to resolve confusion in instances when cases have appeared phenotypically mismatched to historical subtype, or have

Table 1 Phenotypes and *PRNP* variants historically associated with the 3 classical subtypes of genetic prion disease

Clinical Term for Historical Prion Disease Subtype	Classical Symptoms Historically Associated With This Subtype	*PRNP* Variants Historically Associated With This Subtype
Genetic Creutzfeldt-Jakob disease	Prominent early cognitive symptoms: memory decline, dementia; also ataxia, myoclonus, pyramidal and extrapyramidal signs, behavioral change, psychiatric symptoms such as hallucinations, delusions, and depression; rapidly progressive	E200K, D178N-129V, V210I, V180I, M232R
Fatal familial insomnia	Prominent early dysautonomic symptoms: sleep dysregulation, sympathetic overactivity, endocrine abnormalities; also, abnormal gait, weakness, hallucinations, cognitive impairment, dementia; rapidly progressive	D178N-129M
Gerstmann-Sträussler-Scheinker disease	Prominent early motor symptoms: progressive cerebellar ataxia, parkinsonism, muscle weakness; also, cognitive impairment, sensory defects, behavioral change, dementia; slowly progressive.	P102L, A117V, P105L, F198S

Symptoms summarized from Takada et al[27] and Takada et al.[14] This list includes both high-penetrance pathogenic variants and risk factors with low to modest penetrance.[10]

presented differently within a family despite shared genotype.

Some pathogenic *PRNP* variants have historically eluded the framework mentioned earlier, including the OPRI variants. *PRNP* normally has a region of five 24-base pair octapeptide repeats. Although both deletions and insertions can occur, Mendelian segregation is best established for insertions of 5 to 12 repeats. Clinical progression varies widely and is imperfectly predicted by repeat length. Both CJD-like and GSS-like presentations have been reported within a given OPRI family, and mixed CJD-like and GSS-like pathology have been reported even within the same brain, offering further challenge to the diagnostic boundaries between these subtypes.[27]

Rare nonsense variants can also cause prion disease by producing a truncated version of the protein that fails to properly localize to the plasma membrane. These variants tend to present with a longer disease course and highly variable range of phenotypes atypical of prion disease. Some cases are mistaken for Alzheimer disease or behavioral variant frontotemporal dementia owing to their gradual course variably defined by behavioral, cognitive, and motor decline.[14,27] By contrast, a subset of these variants, including R163X, cause a yet more unusual phenotype including sensorimotor neuropathy, chronic diarrhea, and urinary dysfunction, with dementia emerging only late in the average 20-year course. The prominence of peripheral symptoms may raise suspicion of a hereditary sensory and autonomic neuropathy or transthyretin familial amyloid polyneuropathy.[28] This wide variability in the first symptoms of genetic prion disease highlights the critical importance of performing *PRNP* sequencing at the earliest opportunity.

Penetrance in genetic prion disease

As penetrance estimates for *PRNP* variants are continuously subject to update, clinicians should approach the prion disease literature with caution. Some reported variants appear to have low penetrance or be benign despite reports to the contrary in PubMed. Case reports must be approached with the caveat that a variant seen only once or a few times may be a benign bystander in a sporadic case; see Mok et al[29] for an example of how to evaluate such cases consistent with ACMG/AMP guidance. Confidence in pathogenicity can be gained from evidence of Mendelian segregation and/or a convincing enrichment of the variant in cases compared with population controls.[10,12] According to recent studies using these methods, several variants (Figure 1) have evidence of high penetrance, conveying lifetime risk of >90%.[10,12] The 3 most common highly penetrant genetic prion disease variants—E200K, D178N, and P102L—collectively account for 53% of all genetic prion disease cases, and 85% of those caused by a highly penetrant variant.[10]

Certain *PRNP* variants appear to be low-penetrance risk factors, based both on prevalence in cases vs controls and frequency of family history.[10] V210I is the most common such variant, conveying an estimated 10% lifetime risk. The variants V180I and M232R correspond to an estimated 1% and 0.1% lifetime risk, respectively.

Although future analysis of larger case and control data sets may refine penetrance estimates, the overall categorization of the aforementioned variants as high or low penetrance is unlikely to change. More data may, however, enable interpretation of variants seen too rarely in either prion disease cases or the general population to enable a meaningful assignment of pathogenicity thus far. Supplemental Table 1 provides an overview of *PRNP* variants reported to date, including very rare variants, and evidence available at present to support high penetrance and/or increased risk.

Age of onset in genetic prion disease

Age of onset varies dramatically for all genetic prion disease variants (Table 2), and no factors, including sex or parental

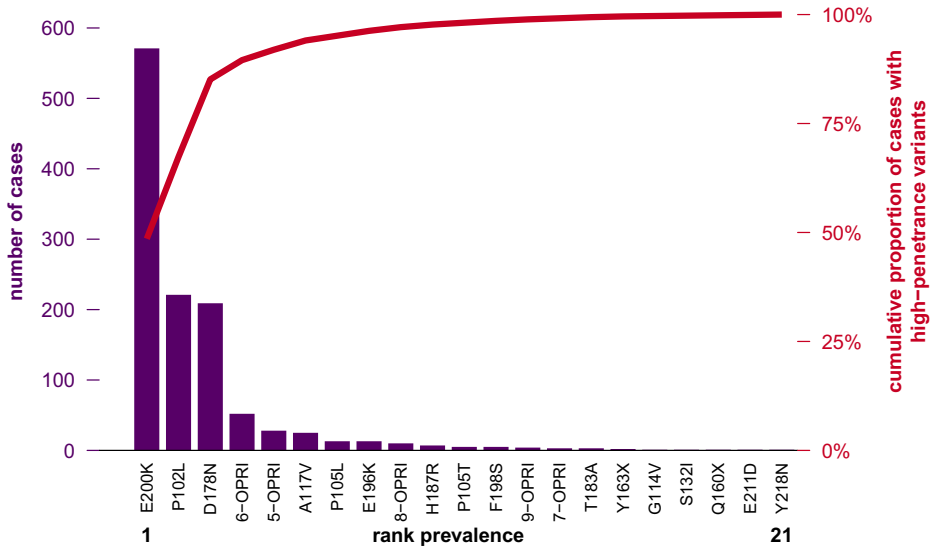

Figure 1 Prevalence and relative contribution to overall case load of highly penetrant *PRNP* variants. Genetic variants with evidence for high penetrance[12] are plotted according to the number of corresponding cases in a case series of 10,460 genetic prion disease patients gathered from prion disease centers in 9 countries. The cumulative proportion of high penetrance cases accounted for by these variants is shown on the right axis. Figure reproduced with permission from https://github.com/ericminikel/prnp_onset/blob/master/figures/figure_s1.pdf, see Minikel et al[12] for details. OPRI, octapeptide repeat insertion.

age of onset, are known to predict it. In families with extensive family history, age of onset variability may be a source of confusion. Families may theorize triggers for symptomatic onset, including a recent stressful incident or medical event. However, there is no evidence to support an environmental, behavioral, or medical trigger for onset of genetic prion disease.

Unlike in Huntington disease, an individual's age of onset does not appear to be predicted by their affected parent's age of onset,[12] including that there is a lack of anticipation or systematic trend toward earlier onset in subsequent generations.[30] Unless raised by the family, introducing the concept of anticipation, even to explain that it is inapplicable, is likely to cause only undue distress.

Rate of progression in genetic prion disease

Notwithstanding significant within-group variation, genetic prion disease variants can be categorized as rapidly progressive (typically progressing from first symptoms to death in less than 3 years) or slowly progressive (total disease duration averaging 3 or more years).[27] Roughly two-thirds of genetic prion disease cases are rapidly progressive, including those caused by the relatively common E200K and D178N variants;[10] 50% of these patients die within 1 year of first symptoms and only a small minority survive to 2 years after onset (Figure 2). By contrast, OPRI variants and those traditionally linked to GSS tend toward a longer disease course. However greater variability in duration for these variants precludes meaningful individual-level predictions. P102L, the most common slowly progressive variant, can correspond to a disease course of 1 year or 15 years. Notably these data are confounded by end-of-life decisions and do not capture when a patient became dependent on intubation or ventilation, which can dramatically extend the nominal course of prion disease.[31]

Founder populations

Some genetic prion disease variants show geographical clustering due to founder effects. The variants V210I and V180I risk factors are more common among those of Italian and Japanese ancestry, respectively, whereas the E200K variant is unusually prevalent among Libyan Jews in Israel and Slovakians.[27] Despite this enrichment, the E200K, D178N, and P102L variants appear to have arisen independently in many populations; all 3 are found around the world.[10]

Genetic Counseling for Prion Disease

Preparing for counseling on prion disease

Despite its rarity, prion disease is well-characterized and resources exist to aid in preparation for counseling sessions. Although care teams must commit to thorough preparation, lack of experience with prion disease per se should not be considered a barrier to providing counseling. Many families must conduct an extensive search to find a provider willing to provide counseling and testing. This article aims to fill this gap by providing the best practices for meeting the needs of these families.

Ideally a multidisciplinary team, including a neurologist, a genetic counselor, and a social worker will have the opportunity to manage genetic prion disease cases together. Key preparation will include understanding the penetrance

Table 2 Age of onset for the 7 most common highly penetrant genetic prion disease variants, ranked by number of cases documented in a case series of 1094 genetic prion disease cases gathered from 9 international prion disease centers

	Without Censored Data		Survival Curve Including Censored Data		
Pathogenic Variant	Mean ± SD	*N*	Median (IQR)	Range	*N*
E200K	61.3 ± 10.0	456	62 (55-68)	31-92	506
D178N	51.3 ± 11.8	256	53 (46-60)	12-89[a]	289
P102L	53.7 ± 10.6	193	56 (47-60)	22-75	206
6-OPRI	35.1 ± 5.8	31	35 (32-39)	23-47	34
A117V	41.2 ± 7.8	26	41 (37-45)	25-58	28
5-OPRI	46.8 ± 6.0	14	49 (44-53)	34-56	18
P105L	46.5 ± 8.5	13	47 (40-51)	31-61	13

Data reproduced with permission from https://github.com/ericminikel/prnp_onset/blob/master/figures/table_1_table_s3.xls, see Minikel et al[12] for details. Censored data refers to individuals who had not experienced onset at last observation.

IQR, interquartile range; *OPRI*, octapeptide repeat insertion.

[a]Denotes a pathogenic variant-positive individual still healthy at age 89.

of the relevant variant, if known, as well the wide range in age of onset and phenotypic presentation associated with all variants. Both families of prion disease patients undergoing *PRNP* sequencing and at-risk individuals considering predictive testing should have before and after test genetic counseling.

Testing

The team should be familiar with testing protocols in prion disease. Because of its technically transmissible nature, most developed countries have a national surveillance center that performs centralized testing for prion disease. In the United States, the National Prion Disease Pathology Surveillance Center in Cleveland, Ohio, routinely handles diagnostic testing, including cerebrospinal fluid real-time quaking induced conversion assay for premortem diagnosis, as well as postmortem autopsy. It also performs targeted *PRNP* sequencing on both symptomatic patients and those at risk. At the time of preparing this manuscript, predictive testing was free of charge for those with a first-degree relative confirmed to have prion disease. Results are returned to an ordering health care provider to be shared with the patient or family. In addition to providing testing, the Surveillance Center serves as a resource and biobank for the prion disease research field and is equipped to receive postmortem tissue should a patient's family wish to donate tissue to research. Although several other clinical laboratories also offer *PRNP* genetic testing either as a single gene test or part of a panel, ordering providers must be mindful of testing techniques and coverage, as OPRIs are not typically detected by next-generation sequencing (NGS). Therefore, unless there is a known *PRNP* point variant in the family, a protocol designed to detect OPRIs, such as gel electrophoresis,[32] allele-specific Sanger sequencing, or long-read sequencing[33] should be employed. Bearing in mind this limitation of NGS, in the event that prion disease is part of a broad differential diagnosis of a neurodegenerative disease and there is a family history of a similar condition, a large NGS dementia panel may be considered as a first step to rule out conditions such as familial Alzheimer's disease or frontotemporal dementia.

Transmission concerns

If raised by the patient or family, providers should be prepared to speak to questions about the horizontally transmissible nature of prion disease. It is crucial to reassure concerned families that misfolded PrP is transmitted from person to person only through extraordinary circumstances such as brain-to-brain contact in the context of a medical procedure.[34] Prion disease is not acquired through any normal activity, including sharing a household, intimate contact, caretaking activities, or routine medical or dental care. In addition, available evidence suggests that individuals with pathogenic *PRNP* variants are healthy for the vast majority of their lives, with prions appearing in the central nervous system only briefly before onset of clinical symptoms.[35] In genetic prion disease families, the disease tracks strictly with the inheritance of the pathogenic variant; there is no evidence to suggest that prions are passed vertically through breastfeeding or pregnancy.[36]

Many blood banks maintain cautious policies regarding prion disease risk and individuals with either a family history of prion disease or known pathogenic *PRNP* variant may be distressed to find themselves ineligible to donate blood. There have been 4 cases of human-to-human transmission of the peripherally acquired prion disease subtype variant CJD after blood transfusion.[37] In the context of genetic prion disease, such prohibitions reflect an abundance of caution rather than an established risk. Blood-based transmission of prion disease has not been reported for any form of human prion disease other than acquired variant CJD, and even at the symptomatic stage of disease, blood is considered a "no detectable infectivity" tissue by the World Health Organization.[38] Risk should be particularly low in asymptomatic individuals at risk for genetic prion disease given that prions are generally not detectable even in their spinal fluid.[35] Therefore, individuals from genetic prion disease families should be reassured that their blood poses no known transmission risk.

Resources

At present, no disease-modifying treatment for prion disease is available. It will be important to convey this information in balance with a high-level overview of the state of the prion disease field. Like many rare diseases, prion disease is profoundly isolating. Families may mistakenly assume that no one else can relate to their plight or that such a rare disease lacks prospects for scientific progress. It is critical to emphasize that despite the rarity of prion disease, the

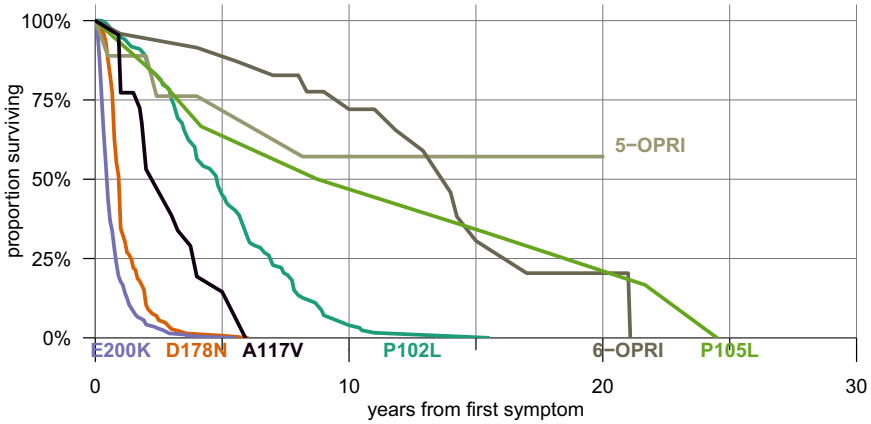

Figure 2 Rate of progression of genetic prion disease for the 7 most common highly penetrant *PRNP* variants. Figure reproduced with permission from https://github.com/ericminikel/prnp_onset/blob/master/figures/figure_s2.pdf, see Minikel et al[12] for details. OPRI, octapeptide repeat insertion.

community of affected patients and families is strikingly well-organized and the disease itself is well-understood by a large and active research community. Genetic counselors and clinicians can refer patients, families, and at-risk individuals to resources available to help them feel less alone, track down answers, and understand the progress being made toward meaningful therapies (Table 3).

Diagnostic genetic counseling session

In many cases, a genetic counseling session may be triggered by a symptomatic case within the family and may occur either before or after the patient has been tested. Given the disease's rapid progression, family members are likely to attend without the proband. Because so many cases lack a family history, families may be referred for genetic counseling without any prior knowledge of either the disease or the attendant genetic risk. By contrast, some families may arrive already expert on a disease that they have witnessed many times.

As with any genetic counseling, sessions should start by determining why the client was motivated to schedule a consultation and what they wish to achieve. Understanding the client's disease experience is essential for providing both the right information and the needed compassion. Families taxed by a long diagnostic odyssey and by the rapidity of their loved one's decline may arrive depleted and learning that the disease could be genetic can come as a shock. Unless genetic counselors take the time to allow their clients to grieve before diving into the genetics of the disease, little will be heard or retained.[39]

When the clients are ready, a detailed pedigree should be taken noting cause and age of death, disease duration, and neurologic and psychiatric history in at least 3 generations. Targeted questions should focus on cognitive impairment, movement disorders (eg, parkinsonism, ataxia), seizures, insomnia, depression, anxiety, personality change, and psychosis. Once obtained, the pedigree can be used to personalize the educational part of the session.

Care should be taken to tailor background explanation to the baseline scientific and medical literacy of the clients, as well as to their specific understanding of prion disease. With that caveat, the informational part of the session should summarize the following:

- Definition of prion, types of prion disease (sporadic, genetic), the pathogenesis of prion disease
- Basic genetics: autosomal dominant inheritance, structure of DNA, variants
- The concept of de novo pathogenic variants, and other causes of missing family history
- Inter- and intra-familial phenotypic variability (presentation, age of onset, duration of disease). Referring to the pedigree to show variability can be helpful.
- If known, specific information about the family variant, especially prognosis and penetrance. Referring to the pedigree to show reduced penetrance and missing family history can aid understanding.
- As individuals try to understand their own risk or that of family members, care should be taken to distinguish between the following:
  - o A priori, there is a 10% to 15% chance that a prion disease case is genetic.
  - o If the case is confirmed to be genetic, there is a 50% chance that a child of an affected parent inherited the causal variant.
  - o If inherited, risk may still be influenced by that variant's penetrance.

After the informational portion of the session, the genetic counselor should assess the family's understanding of the genetic risk. Specific issues to be explored are risk to family members present, sharing of information with non-attending family members, and whether any family members might be interested in predictive testing. The counselor can offer to talk with other family members or write an informational family letter.

Table 3 Resources to support patients and families affected by prion disease

Organization	Mission	Key Activities
CJD Foundation (cjdfoundation.org)	A US-based nonprofit organization with the mission of supporting families affected by prion disease, raising awareness, and supporting prion disease-related medical education and research	The CJD Foundation operates a patient and family helpline, provides educational materials to both families and medical professionals, hosts regular workshops and teleconferences, advocates for prion disease research and surveillance funding, makes research grants, and convenes an annual meeting that brings together affected families and prion disease experts
CJD International Support Alliance	International network of nonprofit organizations committed to improving the lives of prion disease patients and families around the world.	The CJD ISA serves as an umbrella organization for patient support groups around the world, supports patients to connect with care and resources in their country, and supports those interested in starting new patient groups in countries not yet served
Prion Alliance (prionalliance.org)	A US-based non-profit devoted to funding scientific research toward a treatment for prion disease.	Prion Alliance, which is run by patient-scientists personally affected by genetic prion disease, fundraises to support the development of prion disease therapeutics, in addition to maintaining a frequently updated prion disease FAQ; an associated scientific blog, cureffi.org, reviews key topics in prion disease and adjacent biomedical domains, for providers or patients/families interested in engaging prion science in more detail.
Prion Registry (PrionRegistry.org)	A private, secure, global online registry for those affected by prion disease in any way (patients, at-risk individuals whether tested or untested, family and friends who wish to register as controls).	Co-led by the Prion Alliance, CJD Foundation, and CJD ISA, the Prion Registry connects the prion disease community with opportunities to participate in research studies or future clinical trials. Although intake data from each participant remains strictly private, anonymized group-level data from the registry are available to qualified researchers to facilitate therapeutic research and future trials.

CJD, Creutzfeldt-Jakob disease; *FAQ*, frequently asked questions, *ISA*, International Support Alliance.

If genetic testing on the proband has not yet been performed, the possible types of results (positive, negative, variant of uncertain significance) should be explained, as well as the implications for the family. Finally, the genetic counselor should lead the family through a discussion on whether a genetic test on the affected person is in the best interest of that person and the family. Because families may be overwhelmed by having to manage the affected person's needs, alternatives to testing during the lifetime should be offered, including banking DNA and testing future autopsy tissue. If appropriate, an informed consent should be signed. Families should also be provided with the resources listed at the top of this section. The CJD Foundation, in particular, is well-equipped to support those caring for a currently symptomatic loved one.

Predictive genetic counseling for prion disease

In the context of predictive testing, it is important to recognize the wide spectrum of preference present in the at-risk community. The appropriate path for any at-risk individual will need to be determined on a case-by-case basis.

Because prion disease is a fatal neurodegenerative disease, providers should be prepared to follow a modified version of the Huntington disease protocol. In weighing the appropriate level of procedure and caution, genetic counselors will need to listen to the client's needs and preferences, whereas also being sensitive to the factors that are correlated with rare but concerning adverse outcomes after predictive testing: a prior history of significant anxiety or depression, lack of planning for the future, strong identification with the disease that is not adaptable to an unexpected result, a poor support system, or poor communication with family.[40-47] Notably, negative reactions can accompany either a positive or negative result.[43,48] For individuals with either identified risk factors or significant uncertainties about their readiness for testing, access to an evaluation by a psychiatrist familiar with predictive genetic testing for neurodegenerative disease may be helpful.[49-51] If access to psychiatry is limited, genetic counselors may involve another clinician to evaluate the client's readiness. In such cases it may also be reasonable to recommend a minimum 1-month interval between genetic counseling and genetic testing, to allow the client time to process new information and possibly change their mind.[51]

Despite the concern that they generate, adverse reactions to testing are uncommon. The literature consistently shows that most people who undergo predictive testing for a neurodegenerative disease adapt to their results without long-term consequence.[47,51-54] Although some studies report after-test divergence in distress levels between those who test positive and negative, these gaps typically close

within weeks to months.[42,46,55,56] Many people report important benefits from receiving their genetic information, regardless of outcome.[47,57] Relief from uncertainty can be a significant psychological factor, capable of more than compensating for an unwanted result[42,57,58] and the act of gathering information through testing can itself be an effective coping mechanism.[59] A recent study in genetic prion disease echoes the broader finding that although having a genetic disease in the family is stressful, predictive testing does not increase this stress level above baseline.[60] There is some indication that predictive testing rates are gradually rising in genetic prion disease,[61] in keeping with increased rates of genetic testing in neurology clinics in general[62,63] and perhaps reflective of a greater openness to predictive testing among young adults.[64]

Just as some individuals will approach testing with ambivalence, others will approach it with self-knowledge that they wish to access their genetic information—whether to relieve unwanted ambiguity, assert personal control, begin planning for the future, or simply out of a "need to know." The testing protocol should be flexible for clients who understand the disease, lack risk factors for bad outcomes, and are confident that they wish to test. It is important to recognize that whereas some clients may feel pressured by family members or physicians to pursue genetic testing, others may feel pressure to not pursue genetic testing. Regardless, this decision is ultimately the individual's alone.[50] A genetic counselor should be prepared to serve as a buffer against either form of pressure, on a case-by-case basis. For clients with high-risk characteristics, it may be appropriate for genetic counselors to slow the process down until the individual is adequately informed. For others, the genetic counselor may serve the equally critical role of helping to minimize barriers and delays that may themselves become acute sources of stress at an already demanding time.

Predictive genetic testing counseling sessions

Among individuals seeking predictive testing, awareness of family history will vary from multigenerational knowledge to recent first encounters with the disease. Thus, as with diagnostic testing, it is essential to ask about the client's experience with the disease, validate their feelings, and explore their motivation for genetic counseling.

The informational part of the session mirrors a diagnostic counseling session, with special emphasis on the relevant variant's phenotypic variation and the penetrance. It is important for the client to understand that if they test positive, their age of onset and presentation could differ from other family members. The discussion should encompass the Genetic Information Non-discrimination Act (GINA,) life/long-term care insurance, and reproductive options. It can be noted that *in vitro* fertilization with preimplantation genetic testing has been used successfully in genetic prion disease.[65] Creative options around disclosure of results should also be discussed, including nondisclosure *in vitro* fertilization with preimplantation genetic testing (IVF-PGT) and the possibility of depositing DNA or holding a genetic test result in reserve for future use by the client or their family.[50]

In addition to the aforementioned points, clients should be given access to the resources highlighted at the top of this section, and should be introduced to the presence of a well-organized support network and active research community in prion disease. With the preface that participation is always an individual's choice that can be undertaken or revoked at any time, they should be informed that there are opportunities for healthy individuals at risk for prion disease to participate in research. Some clients will feel powerfully motivated to contribute to scientific progress against this disease[57,61] and will be empowered by the knowledge that in a rare disease, every participant's contribution is significant. It is also important to share with clients that as in many brain diseases, research indicates that effective prion disease treatments, once available, will have the greatest impact if given before symptoms arise.[66,67] This understanding has generated momentum for preventive clinical trials in healthy individuals at known risk for genetic prion disease.[66]

The psychosocial portion of the session should be considered anticipatory guidance and is key to helping the client make an informed decision about whether to test. In the spirit of transparency, the client should be informed that most people adapt well to their results regardless of outcome and that factors associated with adverse outcomes include prior significant depression or anxiety, inflexible assumptions about results, and inadequate social support.

The following topics and questions should then be explored:

- How do you imagine a positive or negative result would affect you emotionally over the short-term? Over the long-term?
- In what ways would a positive or negative result change your choices and quality of life?
- How would a positive result affect your significant other, your parents, your siblings, or other key people in your life?
- Do you think it would be useful to you to have a family discussion before testing, to discuss who would want to know your results, and how you would support each other if results differed?
- Would you consider seeing a therapist for emotional support? Do you believe this would be useful for you?

Difficult questions may arise in the discussion of whether results will be communicated to family members. Although there may be an ethical duty to warn, not all individuals will want to do so. Many may be concerned about raising anxiety, particularly in their children. The ideal way of dealing with this issue is for the person being tested to have a discussion with family members before receiving results. They can frame the discussion hypothetically and ask whether the

family member would want to know the result if the at-risk person chose to test. This gives the family members the right not to know and clarifies who to tell. Parents who are hesitant to tell adult children should be forewarned that withholding this information can create unwanted situations such as a pregnancy. Disclosing results to adult children may cause anxiety but gives them the option to pursue their own predictive testing.

Clients are strongly advised to bring a support person with them to both their genetic counseling and result sessions. If present, the following questions should be explored with the support person:

- How do you imagine _____ would respond to a positive or negative test result over the short-term? Over the long-term?
- Are you worried about how they will cope?
- Would you consider seeing a therapist for emotional support? Do you believe this would be useful for you?

These topics often produce emotional responses from the client and from the support person. The genetic counselor should validate their feelings and can also mirror and reinforce signs of strength, resilience and proactiveness that emerge in discussion.[39] They may also need to challenge misconceptions. If serious concerns arise, including signs of significant anxiety or depression or discrepant views that could influence the outcome of testing, the genetic counselor can raise for discussion the options of deferring testing, or providing referrals for individual or couples counseling.

Result sessions

It is highly recommended that at least 1 support person attend the result session. If a client believes it will be a net source of support, result sessions may include multiple family members who can support each other and plan together whether and how to communicate results to other family members. The genetic counselor can offer a family meeting or family letter to aid communication. The genetic counselor conveying results should be empathetic yet straightforward. Time should be given to allow the client to process the results. The counselor may offer to leave the room for a short time. The counselor should offer to answer all questions and explore feelings. The genetic counselor can suggest that an appointment be made with a therapist soon after the session. However, this is a recommendation, not a requirement.[50]

Additional questions about horizontal transmission may emerge at this (or any) session. As discussed earlier, concerned individuals should be reassured that person-to-person transmission of misfolded PrP occurs only under exceptional circumstances and that even at the symptomatic stage, prion disease patients pose no hazard to their loved ones.

A follow-up phone call or in person appointment should be offered the week after the result disclosure to answer questions and address concerns.

Conclusion

Prion disease is devastating for both patients and families. Often a long search for a diagnosis ends with a family receiving the news that their loved one has a rapidly progressive fatal disease. This situation is made worse by either knowing that the case fits the pattern of the family disease or by learning for the first time that the disease could be genetic. Genetic counselors are in the unique position of supporting these families in understanding the disease and in making informed decisions about pursuing a genetic diagnosis. Ideally a multidisciplinary team will work together to understand and support client preferences, identify and minimize sources of distress, share relevant resources, and provide, if appropriate, referrals to mental health professionals. For some at-risk individuals, predictive testing may compound the fear and loss of control already set in motion by losing a loved one to prion disease. For others, it may represent one of the few concrete actions available to combat uncertainty, seize agency, and move forward with their lives. At a difficult crossroads, genetic counselors have a rare opportunity to empower clients and families by providing information, respecting autonomy, and sharing opportunities for proactivity, participation, and connection.

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Conflict of Interest

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Additional Information

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Supplemental Information

Table S1. Evidence for pathogenicity of reported PRNP variants. Four kinds of evidence are provided**:** high penetrance is supported by Mendelian segregation (at least three cases within a family) and confirmed *de novo* variants in cases, while increased risk is supported by enrichment in observed cases versus controls,[1] and observation of cases homozygous for the variant. According to ACMG/AMP guidelines, *de novo* protein-altering variants and case-control enrichment are considered strong and moderate evidence of pathogenicity, respectively.[2] While the guidelines generally designate Mendelian segregation as merely supportive evidence,[2] the knowledge that *PRNP* is the single causal gene in prion disease, with all known pathogenic variants occurring in the protein-coding region, raises the prior that a rare protein-coding variant that seen to segregate with prion disease is causal. Finally, a homozygous rare protein-coding variant in a case, particularly in the context of a negative family history, is suggestive of increased risk that cumulatively reaches clinical significance when two copies of the variant allele are present. Table adapted with permission from cureffi.org;[3] which provides further discussion of evidence types.

*The four octapeptide repeats in human *PRNP* differ in codon choice at the DNA level while being identical at the protein level. Different DNA sequence variants giving rise to the same protein change have been reported in different families, and would have various distinct representations in HGVS nomenclature.[4]

Table S1. Evidence for pathogenicity of reported PRNP variants.

Variant	HGVS	Evidence for high penetrance	Evidence for increased risk	Refs	Comments
P39L	NM000311.5: p.Pro39Leu			4	
2-OPRD	*			5,6	
1-OPRI	*			7,8	
2-OPRI	*			9	
3-OPRI	*			10	
4-OPRI	*			11	most cases have negative family history
5-OPRI	*	Mendelian segregation		12	
6-OPRI	*	Mendelian segregation		13	
7-OPRI	*	Mendelian segregation		14	
8-OPRI	*	Mendelian segregation		14,15	
9-OPRI	*	Mendelian segregation, *de novo*		16,17	
12-OPRI	*	Mendelian segregation		18	

P84S	NM000311.5: p.Pro84Ser			19	
S97N	NM000311.5: p.Ser97Asn			20	
P102L	NM000311.5: p.Pro102Leu	Mendelian segregation	case/control enrichment	21	
P105L	NM000311.5: p.Pro105Leu	Mendelian segregation		22	2 sibs affected & genotyped, 1 ungenotyped parent likely affected
P105S	NM000311.5: p.Pro105Ser			23	
P105T	NM000311.5: p.Pro105Thr	Mendelian segregation		24	
G114V	NM000311.5: p.Gly114Val	Mendelian segregation		25,26	pedigree suggests high penetrance though not 100%
A117V	NM000311.5: p.Ala117Val	Mendelian segregation	case/control enrichment	27	
129insLGGLGGYV	NM000311.5: p.129insLGGLGGYV	*de novo*		28	
G131V	NM000311.5: p.Gly131Val			29,30	positive family history in one case
G131R	NM000311.5: p.Gly131Arg			31	positive family history
S132I	NM000311.5: p.Ser132Ile	Mendelian segregation		32	extensive family history, only proband genotyped
A133V	NM000311.5: p.Ala133Val			33	
R136S	NM000311.5: p.Arg136Ser		2 homozygotes	34	
Y145X	NM000311.5: p.Tyr145Ter			35	
R148H	NM000311.5: p.Arg148His			36	
R156C	NM000311.5: p.Arg156Cys			37	
Q160X	NM000311.5: p.Gln160Ter	Mendelian segregation		38	
Y162X	NM000311.5: p.Tyr162Ter	Mendelian segregation		39	
Y163X	NM000311.5: p.Tyr163Ter	Mendelian segregation		40,41	
D167G	NM000311.5: p.Asp167Gly			42	
D167N	NM000311.5: p.Asp167Asn			43	

Y169X	NM000311.5: p.Tyr169Ter	Mendelian segregation		41	
V176G	NM000311.5: p.Val176Gly			44	
D178Efs25X	NM000311.5: p.Asp178Glufs25Ter	Mendelian segregation		45	only proband genotyped
D178N	NM000311.5: p.Asp178Asn	Mendelian segregation, *de novo*	case/control enrichment	46,47	
V180I	NM000311.5: p.Val180Ile		case/control enrichment	48	
T183A	NM000311.5: p.Thr183Ala	Mendelian segregation		49	
H187R	NM000311.5: p.His187Arg	Mendelian segregation		50	
T188A	NM000311.5: p.Thr188Ala			51	
T188K	NM000311.5: p.Thr188Lys			52	multiple cases with negative family history
T188R	NM000311.5: p.Thr188Arg			52,53	
V189I	NM000311.5: p.Val189Ile			54	
T193I	NM000311.5: p.Thr193Ile			55	
K194E	NM000311.5: p.Lys194Glu			56	
E196A	NM000311.5: p.Glu196Ala			57	
E196K	NM000311.5: p.Glu196Lys	Mendelian segregation		58	only proband genotyped
F198S	NM000311.5: p.Phe198Ser	Mendelian segregation		59,60	
F198V	NM000311.5: p.Phe198Val			20	
E200D	NM000311.5: p.Glu200Asp			61	
E200G	NM000311.5: p.Glu200Gly			62	
E200K	NM000311.5: p.Glu200Lys	Mendelian segregation	homozygote, case/control enrichment	27	
T201S	NM000311.5: p.Thr201Ser			63	
D202G	NM000311.5: p.Asp202Gly	Mendelian segregation		64	only proband genotyped
D202N	NM000311.5: p.Asp202Asn			65	
V203I	NM000311.5: p.Val203Ile		homozygote	66	
R208C	NM000311.5: p.Arg208Cys			20	
R208H	NM000311.5: p.Arg208His			67	

V210I	NM000311.5: p.Val210Ile		case/control enrichment	68,69	
E211D	NM000311.5: p.Glu211Asp	Mendelian segregation		70	supplement describes one family with 3 affected
E211Q	NM000311.5: p.Glu211Gln			58	2 sibs affected
Q212P	NM000311.5: p.Gln212Pro		homozygote	43	
I215V	NM000311.5: p.Ile215Val			71	
Q217R	NM000311.5: p.Gln217Arg			60	2 affected
Y218N	NM000311.5: p.Tyr218Asn	Mendelian segregation		72	
A224V	NM000311.5: p.Ala224Val			73	
Y225C	NM000311.5: p.Tyr225Cys			74	
Y226X	NM000311.5: p.Tyr226Ter			75	
Q227X	NM000311.5: p.Gln227Ter			75	
M232R	NM000311.5: p.Met232Arg			48	
M232T	NM000311.5: p.Met232Thr			76	
P238S	NM000311.5: p.Pro238Ser			77	

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