Fact sheet: Genetic prion disease

About the CJD Support Network

The CJD Support Network is the leading care and support charity for all forms of CJD. The CJD Support Network:

- Provides practical and emotional support to individuals, families and professionals concerned with all forms of CJD
- Provides emotional support to people who have been told that they are at a 'higher risk' of CJD through blood or surgical instruments
- Links families with similar experiences of all forms of CJD
- Offers financial support for families in need
- Provides accurate, unbiased and up-to-date information and advice about all forms of CJD
- Provides a national helpline on all forms of CJD
- Promotes research and the dissemination of research findings
- Promotes good quality care for people with all forms of CJD
- Encourages the development of a public policy response for all forms of CJD
- Provides support, education and training to professionals concerned with CJD

For more information about the activities of the CJD Support Network, contact:

Admin and general enquiries – admin@cjdsupport.co.uk or +44 (0)7494 211476
Support – support@cjdsupport.co.uk or 0800 774 7317
Website – www.cjdsupport.co.uk
Post - PO Box 3936, Chester, CH1 9NG

Registered charity no. **1097173**

Acknowledgements

The CJD Support Network gratefully acknowledges the assistance of Professor Simon Mead of the UK National Prion Clinic, and Professor Richard Knight of the National CJD Research and Surveillance Unit in the preparation of this booklet.

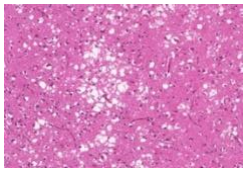
Fact sheet: Genetic prion disease
Version: 3
Date of review: March 2024
Next scheduled review date: March 2026

Contents

Introduction to genetic prion disease

Genetic CJD and Prion Disease (also referred to as inherited or familial prion disease) is one member of a group of rare, progressive, and currently always fatal, brain disorders called the prion diseases. Prion diseases occur in both humans and animals (including BSE in cattle and scrapie in sheep and goats). In this form of prion disease, the cause is an abnormality (mutation) in the gene that is responsible for producing prion protein.

At the molecular level, prion diseases are defined by the accumulation in the brain of an abnormal form of a protein called the prion protein (PrP). PrP can exist in two main forms – the normal form (PrP^{C}) and the abnormal, disease-related, form (PrP^{Sc}). PrP^{C} is a normal body protein that is made in various tissues, especially in the brain, although its normal function is somewhat uncertain. PrP^{Sc} is folded into a different, abnormal, shape compared to PrP^{C}. This misfolding alters its behaviour and it starts to accumulate in deposits in the brain. In association with this, nerve cells (neurons), that are responsible for our normal brain functions, start to become sick and die, causing the symptoms of the disease. The abnormal PrP^{Sc} can cause the PrP^{C} to convert to PrP^{Sc} and this leads to a sort of chain reaction of protein conversion.



Microphotograph of spongiform change in brain tissue taken from a person with CJD.
Courtesy of Sebastian Brander, UCL

The reason for this protein abnormality varies from one form prion disease to another, but, in genetic prion disease, the original cause is an abnormality (mutation) in the prion protein gene (a gene called *PRNP*) which results in the production of a protein somewhat different from the normal PrP and one that is more likely to form PrP^{Sc} and so lead onto disease.

Many different mutations have now been identified and the associated diseases tend to look different depending on the particular mutation involved. There are three broad classifications of genetic prion disease in common use: genetic CJD, Gerstmann Sträussler Scheinker disease (GSS) and Fatal Familial Insomnia (FFI). This classification is based on differences in the clinical features and pathological findings in the brain, but these diseases are all essentially one group: caused by *PRNP* genetic mutations resulting in a prion disease. Experts increasingly tend to use the more general term of 'genetic prion disease' or 'inherited prion disease'.

Genetic prion disease accounts for around 15 per cent of all cases of CJD. There are approximately 10 new cases in the UK each year. Like other forms of prion disease, genetic prion disease typically involves dementia (mental decline with symptoms such as memory loss) and other neurological problems such as unsteadiness and clumsiness. The brain of someone with genetic prion disease generally shows the changes typical of all prion diseases: loss of neurons, spongiform change and the tissue deposition of abnormal prion protein.

Inheriting a risk of prion disease

We all inherit two copies of each of our genes– one from our mother, and one from our father. This includes the prion protein gene (*PRNP*). Both copies could be abnormal, both normal or one normal and the other abnormal. If both copies are normal, then there is no genetic abnormality. In some diseases, one normal copy could be enough for normal function and disease might not result from having one abnormal gene copy. However, in genetic prion disease, one abnormal copy is enough to cause disease. This means that inheriting an abnormal copy from one parent confers genetic risk. In general, either both parents will both have 2 normal *PRNP* copies or one will have one mutated *PRNP* copy (because of the rarity of abnormalities such as this, the chance that both parents would be abnormal is small).

Therefore, for each of their children, there is a 50:50 chance that the mutation will be passed on. This is termed 'Autosomal Dominant Inheritance'. It is important to stress that this is a 50:50 chance on the occasion of each child; for example, it is possible for such parents to have 2 children and either both have the mutation or neither have it.

While the disease is caused by a mutation present from conception, symptoms generally do not start until later in life and, sometimes, even in late life, or not at all. Therefore, affected parents unaware of their own family history, could already have had children before they realize they have a mutation that could be passed on. Sometimes the family history may have not been communicated or genetic prion disease in previous generations may not have been correctly diagnosed. In some instances, variations in the family structure may obscure genetic disease (for example, undeclared different paternity).

Most mutations of the prion protein gene are "fully penetrant" meaning that if a person has inherited the mutation, they will develop the disease in their lifetime, unless they die prematurely of another illness. Some mutations however do not always cause disease in a normal lifetime. This is called "partial penetrance." Do speak to your doctor about whether a mutation found in your family may be partially penetrant.

Can genetic prion disease be transmitted?

Human prion diseases fall into 3 broad groups: genetic (as being considered here), spontaneous (the most common form such as sporadic CJD) and acquired (ie transmitted as an infection). Certainly, while genetic prion disease develops because of a mutated gene and not as a disease caught from animals or other humans, it is potentially transmissible from human to human, but only under exceptional circumstances. The infective agent in prion disease is not a bacteria or virus and ordinary, even intimate, human contact is not a risk.

The only known way that someone with genetic prion disease could transmit the disease to another person is by methods such part of their brain being inoculated into the other person. The risk, therefore, is essentially theoretical in ordinary life or even most medical practice. However, because of public health precautionary concerns, those identified at an increased risk of prion disease, including people at risk of genetic prion disease, are not eligible to donate tissues or blood for use in clinical practice, and should let surgeons know of their situation prior to invasive procedures.

Symptoms of genetic prion disease

The symptoms vary, depending, mostly but not entirely, on the particular *PRNP* mutation involved. There may be great variation in the symptoms within affected members of the same family who all have the same mutation. The symptom pattern in genetic CJD can be similar to that found in sporadic CJD, namely: a fairly rapidly progressive memory and cognition problem, with unsteadiness and clumsiness, and jerky movements (myoclonus). Genetic CJD typically strikes at an earlier age than the sporadic form. The course of the disease is also typically longer, and the patient may survive for several years after the onset of symptoms. The form labelled GSS, usually starts with cerebellar ataxia (unsteadiness and clumsiness) and progresses to dementia at a later stage. The patient may survive for several years. In the form labelled FFI, the presentation is with a progressive and untreatable form of insomnia with other associated features. As the disease progresses, it leads to widespread brain and body dysfunction.

Genetic testing and diagnosis

Clinical diagnosis

PRNP mutations can now be detected in DNA obtained from various sources but typically via a blood test. Clinically ill individuals will have this test as part of their clinical diagnosis. In suspected genetic prion disease, other investigations are the same as for any prion disease. Many tests may be needed (blood tests, brain imaging and cerebrospinal fluid examination) to exclude other possible illnesses. An EEG may show certain characteristic changes and cerebro-spinal fluid protein tests may be helpful. The brain MR Imaging may show diagnostically helpful signs.

As people possess the mutation for years before they become ill, anyone with a relative who has or has had genetic prion disease could therefore opt to have what is called 'predictive' testing to find out if they carry the mutation and are, therefore, at risk of future illness.

Predictive genetic testing

Whether a carrier will go on to develop the disease, and the expected age of onset, depends on the exact mutation. Predictive genetic testing has to be considered carefully because, at present, there is no way of preventing or curing the disease. It requires the individual's fully informed consent, obtained with pre-test counselling and post-test support provided by appropriate specialists, typically Clinical Geneticists. The results will usually have an impact on other family members, and this needs to be taken into account.

Antenatal testing of a foetus at-risk of carrying a *PRNP* mutation is possible. This can give the couple a chance to opt for termination, but this also involves a difficult ethical decision – for a child born carrying a mutated *PRNP* is likely to enjoy normal health for many years before the onset of disease.

There are also possible obstetric/genetic practices that can allow parents to have in vitro fertilization of eggs and select genetically normal embryos for implantation in the womb (pre-implantation diagnosis). This is a complex area, please do raise this with your doctor if you are planning a family.

The diagnosis of CJD in general often takes time, partly due to the lack of a simple straightforward diagnostic test. It is important to stress that a number of neurological conditions can look very similar in the early stages and it is diagnostically helpful, on occasions, to see how the illness develops over time before making a definitive diagnosis. In addition, clinicians do not wish to perform unnecessary distressing investigations on individuals. This time to make diagnosis can be a very distressing period for the family,

particularly as their relative or friend may be deteriorating very rapidly. It is important that clinicians support families and friends through this difficult period and additional support is available from organisations such as the CJD Support Network.

However, in the case of genetic disease with a known family history, the diagnosis may be suspected at an early stage and appropriate investigations undertaken relatively quickly. For those who know themselves to be at risk of genetic disease, any neurological symptoms may cause immediate anxiety and it is important to remember that they may be transient unimportant symptoms or be due to some other disorder and medical advice should be sort without automatically assuming they indicate the onset of CJD.

Is there a cure for genetic prion disease?

At present there is no proven curative or disease-modifying treatment for any form of human prion disease. There are continuing efforts to discover and evaluate potential treatments and genetic prion disease is an important focus for these efforts. Sadly, in the commonest form of human prion disease (sporadic CJD), the disease is often quite advanced at the time of diagnosis, making successful treatment less likely. However, there is the possibility of studying treatments in clinically well *PRNP* mutation carriers with the aim of preventing future illness (although, at this point, nothing is proven to do so).
Further information about possible treatment development can be obtained from the National Prion Clinic (see further information and contacts for details).

Support and care

If hospital admission is arranged, what happens varies, depending on the type of hospital, the particular type of patient and the views of the family. Following admission there will be investigation and tests to establish the diagnosis and general supportive care.

There are a number of drugs which can relieve some of the symptoms of genetic prion disease and make the patient more comfortable – for example, treatments for psychiatric agitation, depression, pain and the jerking movements. General support and care for the patient, family and friends is equally important. Social services should be involved in an early stage to advice on financial matters, respite and long-term care. Various therapists –including speech and language therapists, physiotherapists and occupational therapists – can provide help with specific problems. Community nursing may provide more general nursing care outside of hospital. The National Prion Clinic in London can also provide advice, support and care; this clinic has a particular interest in genetic prion disease and has considerable experience in its diagnosis and management, including the matter of predictive genetic testing and supporting those living with a risk of inherited prion disease. Specialist nursing services are available from the National Prion Clinic and Edinburgh, to provide advice and support for individuals with CJD, their families and also local health professional.

A national care package is able in certain circumstances, to support funding for care. The UK CJD Support Network can also provide advice and support (see their website-details below).

Notification

The Chief Medical Officer has requested that individuals suspected of having CJD should be notified to two organisations, the National CJD Research and Surveillance Unit and the National Prion Clinic. Involvement with these research organisations is entirely voluntary for the patients and their families. Aside from their research functions, these organisations are able to provide additional information, help and advice.

Further information and contacts

Further information about CJD may be found on the CJD Support Network website at www.cjdsupport.co.uk, our fact sheets are also available by post on request to the Network.

Support and information may be obtained from the organisations below:

CJD Support Network

Address – PO Box 3936, Chester, CH1 9NG
Website – www.cjdsupport.co.uk
Phone – 0800 774 7317
Email – admin@cjdsupport.co.uk or support@cjdsupport.co.uk

National CJD Research and Surveillance Unit

Address - Western General Hospital, Crewe Road, Edinburgh EH4 2XU
Website - www.cjd.ed.ac.uk
Phone - 0131 537 1980
Email - contact.cjd@ed.ac.uk

UK National CJD Nursing Service & National Care Fund

Address - Department of Clinical Neurosciences, Clinical Offices, 2nd Floor
50 Little France Crescent, Edinburgh Bio-Quarter, Edinburgh, EH16 4TJ
Website – www.cjd.ed.ac.uk
Phone - 0131 312 0193 / 0131 312 0192
Email - Terri Awe (primary contact) - Terri.awe@nhs.net , Juli Jose (additional contact) juli.jose@nhs.net

National Prion Clinic

Address - National Prion Clinic, Institute of Prion Diseases, Courtauld Building, 33 Cleveland Street, London, W1W 7FF
Website - www.ucl.ac.uk/national-prion-clinic
Phone - 020 7679 5142 / 020 7679 5036
Email - uclh.prion.help@nhs.net