Fact Sheet: CJD and 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

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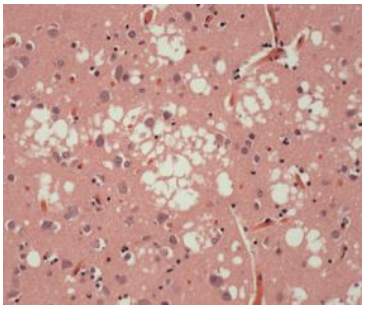
History and Names

The prion diseases are a group of rare, and invariably fatal, brain disorders that occur both in humans and in certain animals. Some of these diseases have been recognized for a long time: scrapie in sheep since around the 1730s, and some forms of human CJD since the 1920s. However, they first came to wide public attention in the 1980s with the appearance of BSE (Bovine Spongiform Encephalopathy) in UK cattle and, subsequently, in 1996, with the identification of human variant CJD.



Microphotograph of spongiform change in brain tissue taken from a person with CJD.

Courtesy of Prof Colin Smith, University of Edinburgh.

The naturally occurring prion disease of sheep and goats is named 'scrapie'. Other forms of prion disease have been named according to the species affected (as in BSE), or specific clinical features (as in Chronic Wasting Disease of deer species) or according to the names of the first describers (as in Creutzfeldt-Jakob disease). Because these diseases produce a spongy state in the brain, they also have been called 'spongiform encephalopathies' ('encephalopathy' means 'disease of the brain').

Some (not all) of these diseases are naturally transmissible and most can be transmitted in certain animal experiments, hence they have also been termed TSEs (Transmissible Spongiform Encephalopathies). It has become clear that these animal and human diseases share a common underpinning: an abnormality in a specific protein-the prion protein. As a result, the generally preferred modern term is 'the prion diseases'.

CJD (Creutzfeldt-Jakob Disease) is named after two doctors (Hans Creutzfeldt and Alfons Jakob) who published papers in the 1920s. While it has been shown that Jakob did indeed describe the disease that we recognize as CJD today, most modern commentators think that Creutzfeldt did not. However, the joint name persists in use. The human prion diseases have been divided into three main types: Sporadic (of uncertain cause), Genetic (inherited) and Acquired (as infections). The tables below list the main recognized prion diseases of animals and humans.

Human Prion Disease	
Genetic	Genetic CJD
	GSS (Gerstmann-Sträussler-Schenker Disease)
	FFI (Fatal Familal Insomnia)
Sporadic	Sporadic CJD
	VPSPr (Variably Protease Sensitive Prionopathy)
Acquired	Variant CJD (originally due to BSE)
	Iatrogenic CJD

Animal Prion Disease	Species Affected
Scrapie	Sheep & goats
CWD (Chronic Wasting Disease)	Certain cervids
BSE (Bovine Spongiform Encephalopathy)	Cattle
FSE (Feline Spongiform Encephalopathy)	Felines, including domestic cats
TME (Transmissible Mink Encephalopathy)	Mink
Prion Disease of Dromedaries	Dromedaries

The Prion Protein and its Gene

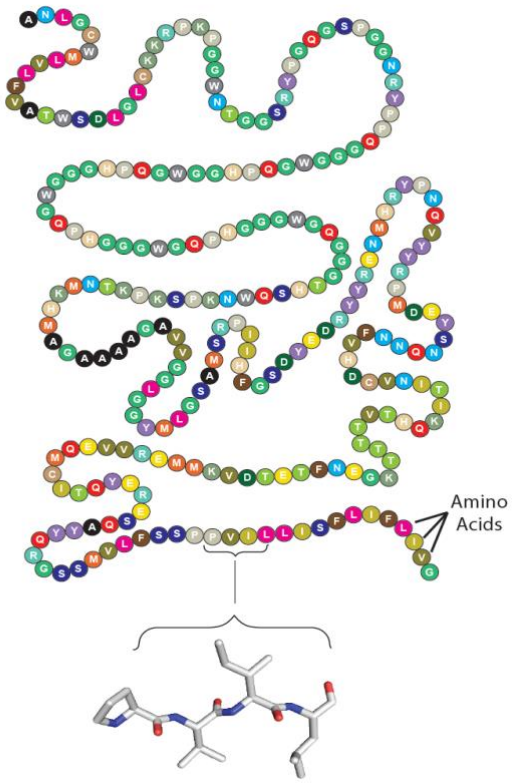


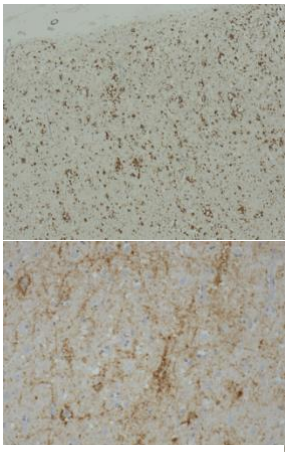
Figure 1 *The 253 amino-acid chain of the human prion protein. Proteins are made of chains of any of 20 amino-acids found in humans. These are shown by letter codes. The molecular structure of a few amino-acids is shown at the bottom of the image. The exact sequence of amino-acids determines how a protein folds, and its function.*

Courtesy of Richard Newton & Lazslo Hozzu.

The prion protein is one of many normal proteins found in animals and humans. Proteins are important molecules that have structural and functional roles in the body. Like proteins in general, prion protein is constantly being made in cells, performing certain functions and then being destroyed, to be replaced by new protein molecules. It is important to realise that the prion protein itself is a normal, important, part of all of us. Its precise normal functions are not agreed but several important roles have been suggested. Proteins are made using instructions from genes. Like all proteins, the prion protein has its own gene: the Prion Protein Gene (In humans, this gene is denoted by *PRNP)*.

In essence, a gene is a string of code, made up of small units (called codons) which, for convenience, are numbered from left to right. In effect, each codon is an instruction to use a small molecule called an amino acid with the overall result of producing a string of amino acids-this is the basic form of the resulting protein-a chain of amino acids. After this process, the basic protein chain is modified in various ways to produce a folded 3D structure and this final structure governs the protein's function. In the case of prion protein and *PRNP,* 253 codons lead to a basic protein structure 253 amino acids long. As well as the basic amino acid chain being folded into a certain shape, there are other modifications, including the addition of sugar molecules. A prion protein may have no, one or two sugar molecules added.

The molecular hallmark of prion disease is an abnormality in the prion protein. The abnormality relates to the folding of the protein chain and its final folded shape. This misfolded form then has different physical and chemical properties to the normal protein form. In particular, it is less soluble, more resistant to being broken down by protein degrading processes and it tends to aggregate into collections of protein that are then deposited in body tissues. A very important property of the abnormally folded protein is that it is able to convert normally folded prion protein into abnormally folded protein; there is, therefore, a progressive increase in the amount of abnormal protein, once it is present.



Prion protein deposition in brain tissue taken from a person with CJD.

Courtesy of Prof Colin Smith, University of Edinburgh.

The obvious next question is then: why does misfolding occur in the first place? There are three broad answers, corresponding to the three main types of prion disease:

1. An abnormality in the gene code causes a different amino acid chain to be formed that is then more likely to fold incorrectly. This is the general explanation of genetic prion disease; it is the result of an abnormal gene.
2. In acquired prion disease, abnormally folded prion protein is introduced into the body in the diet or by medical procedures. This causes the infected individual's prion protein to misfold.
3. Misfolding might occur as a simple accident. Protein molecules are being made all the time, then processed and folded. If a random error occurs and abnormally folded prion protein is produced, it might then go on to convert other normal prion protein. Currently, this is held to be the most likely (but not proven) explanation for sporadic prion disease.

Two points should be made about *PRNP*, the relevant gene:

1) Important errors that cause genetic disease are the result of mutations in the gene code that are inherited. Each of us has two copies of each gene in our body cells: one copy from our father and one from our mother. We, therefore, have a maternal and a paternal copy of *PRNP* in our body cells. In the case of genetic prion disease, one abnormal copy is enough to cause disease. Therefore, if an individual has genetic prion disease due to a *PRNP* mutation, one of their parents should have contributed the abnormal gene. In addition, if that individual has a child then there is a 50:50 chance that they will pass on the abnormal gene. This is called 'Autosomal Dominant Inheritance'.

2) There are variations in gene codes that do not cause disease but which may or may not have other effects. These are called 'polymorphisms'. At codon 129 of *PRNP,* there is a common polymorphism where the code is of one of two types, selecting either for an amino acid referred to as 'M' or another one referred to as 'V'. As all of us have two gene copies, there are three possibilities, depending on what our parents had:

    - We have one with the 129-M code and one with the 129-V code (129MV).
    - We have two, both with the 129-M code (129MM).
    - We have two, both with the 129-V code (129VV).

About half the UK population are MV, about 11% VV and about a third MM. This does not, in general, matter and these variations do not cause disease. However, the variations do have effects on how likely one is to develop prion disease and what it is like if one does.

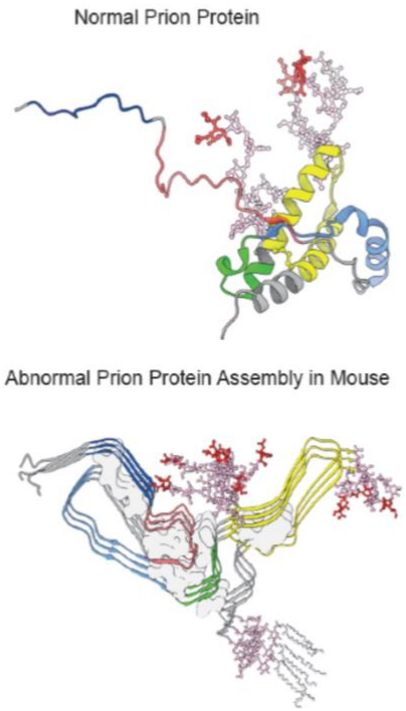


Figure 2 Normal prion protein and the abnormal (prion) form in mouse. These shapes show the way that prion protein is folded and its attached sugars. Normal proteins fold into sheets, loops and twists in a defined way (left). The abnormal or prion form is folded completely differently (right). We believe that the prion protein form has to be stabilised by multiple prion proteins in a stack.

Courtesy of Szymon Manka, Richard Newton & Jonathan Wadsworth.

Infections and the Prion

When prion diseases are acquired, as infections, there must be an infectious agent responsible for transmission of disease. This infectious agent has been termed the 'prion' and it consists either entirely, or mostly, of abnormally folded prion protein. However, its exact structure is not fully determined. Prion infectivity is difficult to eradicate: many usual decontamination and deactivation techniques, that deal with common bacteria and viruses, are poorly effective.

Different prion diseases are characterised by different clinical profiles and varying transmissibility these characteristics are generally preserved on transmission. For example, variant CJD has a particular clinical profile and when it has been transmitted (via blood transfusion), the infected individual develops characteristic variant CJD, not some other prion illness. In bacterial and viral diseases, this is also true. For example, the measles virus cause measles, not mumps. In bacterial and viral diseases, this ability to pass on the same illness is due to information in either the RNA or DNA contained within the bacterium or virus. Indeed, we have all just lived through the Covid epidemic with announcements that different strains of Covid developed, with some variations on the original infectivity and clinical results; these strains behaved differently because of differences in their DNA. In the case of prion diseases, it is thought that the different strains reflect different abnormal prion protein structures, which behave differently.

Some comments on Human Prion Disease and Infections

- While most prion diseases are potentially transmissible, most human prion diseases are not natural infections. Their potential transmissibility is demonstrated by specifically designed laboratory experiments or by accidents that relate to very specific routes (for example, during neurosurgery or via cadaveric-derived human growth hormone).
- The commonest form of human prion disease, sporadic CJD, is not considered to be acquired by infection, but by a random protein mistake (as mentioned above).
- Similarly, genetic prion disease is due to an abnormal gene, and is not acquired by infection.
- Ordinary, even intimate, contact with a person with CJD does not carry a risk of catching the disease. Transmission of prion disease from person to person occurs only in very special circumstances.
- The only human prion disease that is considered a zoonosis (that is, contracted from animals) is variant CJD.

The Disease Process

Prion diseases affect the central nervous system, mainly the brain. The symptoms are, therefore, essentially ones of brain dysfunction.

The pathological features of prion disease include loss of neurons and deposition of abnormally folded prion protein in the brain tissue. Neurons are one of the main cell types found in the brain. They are electrically active, connected to each other and form circuits. The activity in these circuits is responsible for all of our brain functions (sensation, movement, thinking, talking etc). Therefore, all of these may be affected in prion disease. The precise picture varies somewhat with disease (so, for example, variant CJD is somewhat different from sporadic CJD) but also with individual (for example, as detailed above, the *PRNP*-129 polymorphism may affect the way in which the illness presents). However, there are a few particularly common features:

1. Impairment of memory, thinking, language and behaviour, resulting in dementia.
2. Impairment of co-ordination and balance.
3. Involuntary movements, in particular jerking movements called ‘myoclonus’.

While these clinical features result from the dysfunction and death of ‘neurons’, the precise relationship between this on the one hand, and the prion protein misfolding, aggregation and tissue deposition on the other, is not yet completely clear.

Sadly, the disease process is progressive, often rapidly so, and these illnesses are, currently, inevitably fatal and without cure.

Diagnosis

An absolutely definite diagnosis of a human prion disease requires a neuropathological examination of brain tissue. Very rarely, in certain specific situations, this may be done on a biopsy of the brain in life. However, mostly it would be done from tissue examined at autopsy. The presence of deposited abnormal prion protein in the brain tissue is the key diagnostic hallmark.

However, a confident, highly probable, clinical diagnosis is achievable in life in most cases. The clinical features, along with test results generally allow doctors top exclude other possible illnesses and to positively diagnose prion disease. Details of diagnosis are given in our specific disease information sheets.

It should be stressed that the presenting features of prion disease are non-specific, i.e. they may occur in many other diseases and it can take time for tests to be done and a firm diagnosis made. This is important not least because some other diseases might be treatable and need to be excluded

Further information and contacts

Further information about CJD may be found on the CJD Support Network website at www.cjdsupport.net 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

Admin and general enquiries - admin@cjdsupport.co.uk
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

National CJD Research and Surveillance Unit

Western General Hospital, Crewe Road, Edinburgh EH4 2XU
Website - www.cjd.ed.ac.uk
0131 537 1980 telephone number for general enquiries and loth.securecjd@nhslothian.scot.nhs.uk for Care Team enquiries/patient families

National Prion Clinic

National Prion Clinic, Institute of Prion Diseases, Courtauld Building, 33 Cleveland Street, London, W1W 7FF.
Helpline for National Prion Clinic - 020 7679 5142 / 020 7679 5036
uclh.prion.help@nhs.net