CREUTZFELDT-JAKOB DISEASE AND GENETIC TESTING:
Information for Patients & Families

Note: *Definitions for terms in italics can be found in the Glossary on pages 4 & 5*

What is Creutzfeldt-Jakob Disease (CJD)?

- *Creutzfeldt-Jakob disease* (CJD) is a rare, progressive, fatal neurological disease. It usually begins in middle to late adulthood, and leads to rapid degeneration of the affected person's physical and mental capacities.

- CJD is the most common form of a group of conditions known as *prion diseases* (pronounced "pree-on"), which occur in both humans and animals. The hallmarks of prion diseases are certain kinds of microscopic changes that lead to a sponge-like appearance of the brain tissue. These changes can only be confirmed by direct examination, usually *postmortem*.

What are the symptoms of CJD?

- The signs and symptoms of Creutzfeldt-Jakob disease are variable, and may not be immediately recognized by family members or physicians. Initially, an affected individual may appear disorganized, lose interest in their day-to-day activities, and experience memory lapses. These signs are often attributed to depression, therefore the diagnosis of CJD is not always obvious at this point.

- Difficulty with balance and coordination causes a hesitant or unsteady walk; deterioration in eyesight may result in double vision or failure to recognize everyday objects; speech may become slower and more slurred. Soon, affected individuals lose awareness of their surroundings and become dependent on others for their care. In terminal stages, patients may lose bladder control, experience uncontrolled movements (spasms and/or shaking), and eventually lose their ability to speak or move. However, not all individuals with CJD have identical symptoms or length of illness.

- Severe pain or physical discomfort does not appear to be a major feature of the illness.

- At present, nothing can be done medically to cure or treat the condition. The disease is always fatal, and supportive care is the only available option. Most affected individuals succumb within 6 months after symptoms first appear, although in a minority of people, the illness can last more than two years.

- An even rarer form of hereditary human prion disease, called *Gerstmann-Sträussler-Scheinker syndrome* (GSS), tends to produce some symptoms that differ from those of *sporadic CJD*. Examples include severe inability to sleep, pronounced difficulty in walking, slower progression, and a different pattern of microscopic brain changes.

What causes CJD?

- *Proteins* are essential components of the body and carry out diverse activities necessary for life. Prion diseases are caused by an abnormal accumulation in the brain of a specific protein called *PrP* (*Pr*ion *P*rotein).

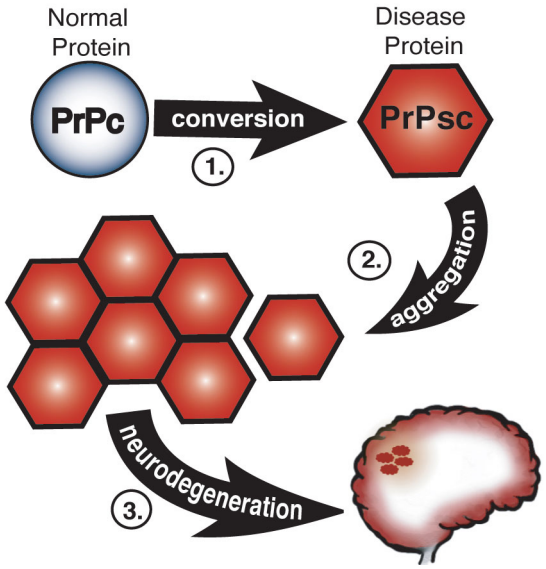

Fig. 2 – Normal protein converts to disease causing protein, and replicates causing spongy holes in the brain.

- PrP in its normal form, PrP^{C}, is naturally present in most cells throughout the body, though its exact role is not well understood. In individuals affected with CJD, some of the PrP^{C} is converted to an abnormally shaped form called PrP^{Sc}. The formation of PrP^{Sc} appears to be harmful in some way to brain cells, and almost certainly is responsible for the *neurodegeneration* that occurs in prion diseases.

- In approximately 85-90% of individuals with CJD, there is no specific cause or *risk factor* (such as diet, occupation, or heredity) that can explain the development of the disease. This is called *sporadic CJD* and appears to occur at random in most human populations, affecting on average 0.5-1 person per million per year, mostly over the age of 50. The occurrence of sporadic CJD in one member of a family does not mean that other members of that family are at increased risk for the disease.

- Hereditary factors explain the disease in most of the remaining 10-15% of persons with CJD. In these cases, alterations (or *mutations*) in a gene called *PRNP*, which carries the biological instructions for making the protein PrP, are responsible for the development of CJD. If such a mutation is found in an individual with CJD or a CJD-like disease, this is considered to account for the condition. All cases of GSS are traceable to such mutations.

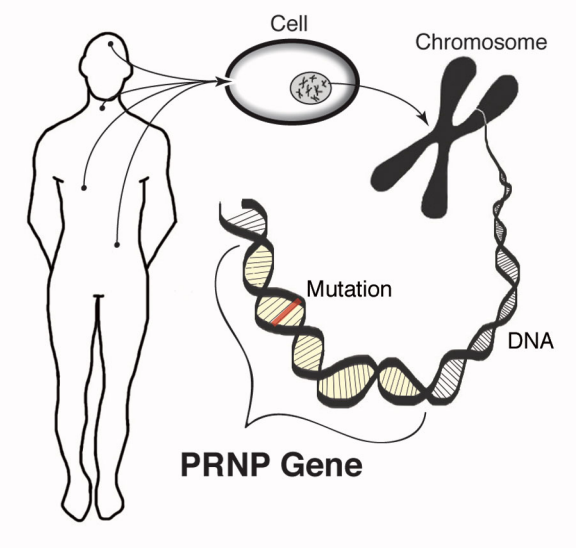

Fig. 3 – *PRNP* gene mutations in a person's DNA are responsible for causing hereditary (or familial) CJD .

- A very small number of CJD cases have resulted from infectious transmission from person to person. This has happened only under very unusual circumstances where accidental (*iatrogenic*) contamination of materials occurred. Such cases involved donated nervous-system tissue (*dura mater*) and hormone preparations that in the 1970s and early 1980s were prepared from donated *pituitary glands*. Since 1985, these hormones have been produced synthetically and carry no risk for transmission of CJD. Despite extensive study, there has never been a case of CJD in Canada traced to contaminated hormone preparations, although there have been some cases related to dura mater grafts. There is no evidence that CJD can be transmitted from person to person through normal physical contact among family members or friends, or between a patient and hospital caregivers.

- A new type of human prion disease called variant CJD (*vCJD*) was discovered in 1996. Since then, it has been responsible for a relatively small number of human deaths in the United Kingdom, France, Italy, Northern Ireland, United States and Canada. A single Canadian case of vCJD was detected and reported to Canada's CJD surveillance system (CJD-SS) in 2002. However, health officials determined that the affected individual acquired the disease during a prolonged stay in the United Kingdom. Since its inception in 1998, Health Canada's comprehensive surveillance program has not detected any vCJD cases of Canadian origin. Although much remains unknown about this new prion disease, it is thought to result from human exposure (most likely food-related) to cattle afflicted with a prion disease called bovine spongiform encephalopathy (BSE) – more widely known as "mad cow disease".

How is CJD transmitted in families?

- It is important to remember that in most cases, CJD is sporadic, meaning that it is not associated with any specific, known risk factor. However, in *hereditary (*or *familial) CJD* the altered gene responsible for an affected person's disease may also be present in some family members who are presently healthy. As CJD tends to appear only in later adulthood, some people with the altered

gene may unknowingly pass it to one or more of their children.

- The *PRNP* gene, which carries instructions for making the normal prion protein PrP, is carried by everyone in two copies (one from each parent). In hereditary CJD, disease is expected to eventually result if only one of these two copies is altered by a mutation. *Carriers* face a high risk of developing the disease during their lifetime, although it is impossible to predict when this will happen.

- The closer one's degree of *genetic* relationship to a person affected by hereditary CJD, the greater one's own risk will be. This means, for example, that a child, brother or sister of a patient with hereditary CJD has a 50% chance (1 in 2) of also carrying the mutation. For a niece or nephew of the patient this chance would be 1 in 4, and for a family member related only by marriage, zero. Almost always, only one of a pair of parents will be a carrier, so that one side of a family will be affected and the other not.

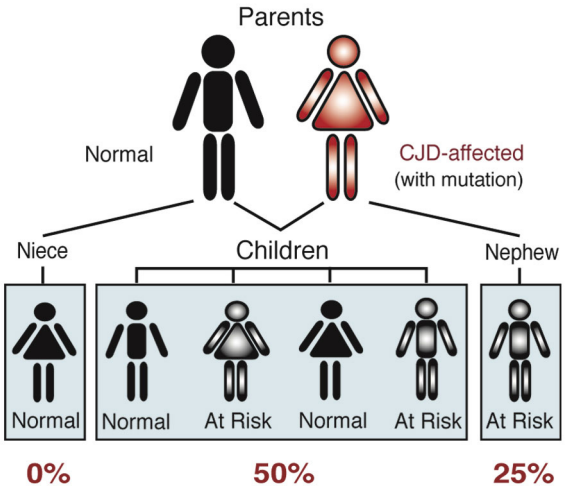

Fig. 4 - Risk of hereditary (or familial) CJD decreases with more distant genetic relationship to an affected person.

How do I know if hereditary CJD is present in our family?

- A test for hereditary CJD is available through Health Canada's CJD Surveillance System. The analysis is done using a standard blood sample. This test is able to distinguish decisively between hereditary and sporadic CJD.

- If you or an affected family member are suspected to have CJD and are asked to enroll in the CJD Surveillance study, you will also be asked whether you wish to have the genetic test performed. Genetic counseling is recommended both before choosing, and after the testing takes place.

- Because a complete analysis of the DNA sequence of the *PRNP* gene is carried out as part of this test, it can detect any known mutation in the *PRNP* gene, as well as those exceptionally rare mutations that are unique to a particular family and thus have not been reported previously in any other CJD patient.

- The majority of genetic tests on CJD patients prove to be negative for the presence of hereditary mutations. Therefore, it is extremely important that testing be completed on the patient first, before undertaking any testing of family members who are presently healthy.

- Three possible results can emerge from a genetic test for hereditary CJD:

1. ***No PRNP gene mutation is found.*** Most of the time, an individual with CJD will not have any abnormalities in the *PRNP* gene. If no such changes are found, then the disease is not considered hereditary. Thus, there is no more risk of acquiring CJD for the patient's family members than there would be for a non-relative, and further genetic testing is not recommended.

2. ***A PRNP gene mutation is found, of a type known to be associated with hereditary CJD.*** If such a change is found in the affected individual, then the disease is determined to be hereditary CJD. Other family members are at increased risk for developing the same condition. At this point, testing would be made available to at-risk family members who wish to determine whether they carry the same mutation.

3. ***A PRNP mutation of unknown significance is found.*** As genetic testing for hereditary CJD has been carried out on behalf of more families, a very small number of individuals

with CJD have been found to carry extremely rare mutations in the *PRNP* gene. These mutations are so rare that either they have simply not been seen before, or they have been seen but there have not been enough families studied to know whether they actually cause CJD. In such cases, the genetic change may in fact be the cause of the affected person's disease. However, until more is known it is not possible to decide that the change is not one of the many variations that occur in human DNA but have no special significance for health or disease. In a case such as this, again genetic testing of family members is <u>not</u> recommended. An exception would occur if new information comes available, such as additional medical reports from other families, or association between the mutation and CJD.

What else should I know about genetic testing?

- Participation in genetic testing is always completely voluntary.
- Genetic counseling is recommended to discuss potential benefits and drawbacks of the genetic test. Such counseling is also the only way to reliably identify additional family members who may be at risk. A genetic counselor will ask questions about your family history. They will also discuss in greater depth the issues involved in genetic testing.
- The main purpose of the genetic test is to distinguish between hereditary and non-hereditary forms of CJD, as hereditary CJD may not be obvious from an affected individual's medical and family history alone. In hereditary cases, other family members may be at risk for CJD. These individuals may wish to pursue testing to know if they carry a *PRNP* mutation.
- The result of the genetic test for hereditary CJD does not change the approach to caring for the affected patient. Genetic testing is not presently able to help predict how long the illness will last, or what symptoms will appear.

Where can I get more information?

Medical genetics specialists are available in most major health-care centres in Canada. Here, physicians and counselors will be able to provide you with more information on genetic testing in affected individuals and relatives who may be at risk for hereditary forms of CJD. If you require more information on how to contact a genetics specialist in your area, you may call the Canadian CJD Surveillance System toll-free at 1-888-489-2999. The brochure you are reading is also available online at:

www.hc-sc.gc.ca/pphb-dgspsp/hcai-iamss/cjd-mcj/

Glossary

BSE: Bovine Spongiform Encephalopathy, a *prion disease* in cattle, first described in 1986 and widely known as "mad cow disease". Exposure to meat products infected with BSE has been linked to human occurrences of *vCJD*.

Carrier: A person whose DNA contains a *gene* with a disease-causing *mutation*, but who does not presently suffer from the disease.

CJD: Creutzfeldt-Jakob disease, the most common form of human *prion disease*.

Hereditary (or familial) CJD: Any of a number of forms of CJD that are caused by *mutations* in the *PRNP* gene.

Iatrogenic CJD: CJD resulting from accidental infectious transmission from person to person, in a medical setting.

Sporadic CJD: The most common form of CJD, for which specific *risk factors* are unknown.

vCJD: Variant Creutzfeldt-Jakob disease, a new form of human *prion disease* first discovered in 1996. It has occurred in residents of the United Kingdom, France, Northern Ireland, Italy, United States and Canada and is linked with exposure to BSE.

DNA: Deoxyribonucleic acid, the chemical compound of which human *genes* are composed.

Dura mater: A human-derived tissue material used for repair after neurosurgery, which has been a vehicle for iatrogenic *CJD* in the past.

Gene: A segment of a *DNA* molecule, which carries coded information for the structure of a *protein*.

Genetic counselor: A medical professional who specializes in assisting patients and families who are affected or at risk of a hereditary medical condition. They help patients and families in understanding their situation, the risks and benefits of *genetic testing*, and the implications of genetic test results.

Genetic testing: A process of medical diagnosis that identifies a disease associated *gene mutation* and determines whether an individual carries it.

GSS: Gerstmann-Sträussler-Scheinker syndrome, a very rare hereditary human *prion disease* with some features that distinguish it from CJD.

Hereditary trait: A characteristic caused by variations in *DNA* that are passed from parent to offspring.

Mutation: An alteration in the structure of a *gene*, which can in turn modify the structure of a *protein* encoded by the gene, which in turn can cause disease.

Neurodegeneration: A progressive disease process involving loss of integrity in cells and tissues of the nervous system.

Pituitary Gland: A small organ found at the base of the brain, which produces various substances required for normal growth and function of the body.

Postmortem examination: A series of tests carried out on a patient's body after death, to confirm cause of death and/or to study a disease

Prion disease: Any of a family of fatal neurodegenerative conditions affecting humans or animals, that are caused by pathological changes in the brain involving a specific *protein* called *Pr*ion *P*rotein, or PrP. Prion diseases involve rapid mental and physical decline, and are eventually fatal.

PRNP: The *gene* that carries the information for the human prion *protein*.

Protein: Any of a large number of different chemical molecules that are made by all living things, and carry out the biological work of cells and tissues. Humans have tens of thousands of different kinds of proteins, each of which is specified by a *gene*.

PrP^{C}: The normal, non-disease-causing form of the prion *protein*.

PrP^{Sc}: The abnormal, disease-causing form of the prion protein.

Risk Factor: A characteristic of an individual, or something to which he or she is exposed, that increases their chances of experiencing disease.