

Kaitlin Olson
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Professor Brutlag
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Fatal Familial Insomnia and the Prion Protein

Fatal Familial Insomnia is a genetic prion disease, exceedingly rare, in which affected individuals appear to die from lack of sleep. In reality, their insomnia is a symptom of the larger prion disease, which causes neural death in the thalamus, resulting in amyloid plaques of aggregated prion proteins, which is characteristic of all prion diseases, although not always in the thalamus. Prion diseases are caused by the prion protein, known as PRNP, of which little is known about its exact function. What has been decided though, is that the prion is a misfolded protein that has the ability to infect the normal proteins about it, causing a chain reaction that destroys neurons in the individual. Other prion diseases include Creutzfeldt- Jakob disease, Gerstmann-Straussler-Scheinker disease, bovine spongiform encephalopathy (Mad Cow Disease), kuru (CJD in natives of Papua New Guinea), and scrapie (in sheep).

Fatal Familial Insomnia is an autosomal dominant disease, meaning that one with an affected parent has a 50% chance of inheriting the disease, which has 100% penetrance—if one inherits the bad allele, one will develop the disease. Fatal Familial Insomnia, at its onset, includes symptoms such as sweating, fever, shrunken pupils, a stiff head, high blood pressure, elevated pulse, and an inability to sleep (Max xiv). The disease range lasts anywhere from 7 to 25 months until the ultimate death of the patient, although it averages at 13 months (“Fatal Familial Insomnia; FFI”). Fatal Familial Insomnia usually strikes individuals in middle age, anywhere from 37 to 61 years of age, although there have been notable cases of younger patients (“Fatal Familial Insomnia; FFI”). With

respect to Darwin's theory of natural selection, the disease strikes after reproduction, which allows the disease to continue and proliferate, instead of being selected against. In the end stages of the disease, the patient develops myoclonus and eventually falls into a coma, followed by death ("Fatal Familial Insomnia; FFI"). Subsequent studies of the brain, after death, show astrocytosis in the thalamic nuclei ("Fatal Familial Insomnia; FFI"). Although insomnia has become an increasingly common diagnosis, the insomnia of individuals with Fatal Familial Insomnia is indicative of the neuron death in the thalamus, which controls functions such as sleep and consciousness. As a result, affected individuals do not technically die of lack of sleep, which is an almost romanticized notion of the disease, but rather the insomnia is simply a symptom of the larger prion disease causing the aggregates that cause neural death in the thalamus. The rarity of the disease, with around 40 families worldwide suffering from the genetic variant, blocks, to some extent, the cure for the disease; it is not pervasive enough for governments to funnel millions of dollars into research. As a result, the disease remains incurable. Although the location of the gene allows for novel diagnosis through genetic testing, there remains no effective medication (although several have been tried) and certainly no cure.

Prion diseases are caused by the prion protein, which is found in all humans. The prion protein is thought to have two structures: the normal and the infectious, malignant protein. Once one prion protein changes to the malignant, it causes a chain reaction when the malignant, misfolded protein bonds with a healthy protein and it in turn bonds with another (Max xxvi). The gene for the prion protein, and therefore prion diseases, is found on Chromosome 20, exactly at 20pter-p12 ("Fatal Familial Insomnia; FFI"). On a molecular level, Fatal Familial Insomnia is caused by a substitution in the amino acid

from asp178-to-asn (D178N) in conjunction with the polymorphism of methionine at 129, abbreviated to met129 (“Fatal Familial Insomnia; FFI”). Although the D178N mutation is often found in victims of Fatal Familial Insomnia, it is not always necessarily present; the disease can occur, particularly sporadically, without it (“Fatal Familial Insomnia; FFI”). The met129 polymorphism is unique to Fatal Familial Insomnia; in Creutzfeldt-Jakob disease, the polymorphism is the change to valine at 129 (“Creutzfeldt-Jakob Disease; CJD”). Individuals who are homozygous for the met129 allele (MM) have been found to have a shorter duration of the disease; the met129 polymorphism has also been found in individuals with sporadic onset of the disease (“Fatal Familial Insomnia; FFI”). There is also a difference in symptoms between those homozygous and heterozygous for met129. In homozygous patients, there were more prominent oneiric episodes along with severe insomnia, and dysautonomia (“Fatal Familial Insomnia; FFI”). In heterozygous patients (met129/val129) severe ataxia and dysarthria at disease onset occurred, along with seizures and early sphincter loss; the duration of the heterozygous form of the disease usually lasted two years (“Fatal Familial Insomnia; FFI”). Clearly, there are several distinct polymorphisms that are convincingly linked to Fatal Familial Insomnia, as there are in other prion diseases, which is what mainly makes them distinct from one another.

Other prion diseases, such as Creutzfeldt-Jakob disease and Gerstmann-Straussler-Scheinker disease, also have distinct changes at the molecular level in the form of polymorphisms. As previously mentioned, Creutzfeldt-Jakob disease is caused by a variant polymorphism to val129, which can similarly be found in affected individuals with Fatal Familial Insomnia, although only in heterozygous form (“Creutzfeldt-Jakob

Disease; CJD”). Symptomatically, individuals with Creutzfeldt-Jakob acquire jerky movements and an unsteady gait along with dementia, characteristic of all prion diseases, due to the deterioration of the neurons in the brain (Max 48). Although little is known about the prion protein, it has been posited that it aids in memory (Max xxvi). Pathologically, victims of Creutzfeldt-Jakob disease are found to have “regions of dead cells and astrocytes,” which are star-shaped cells, which is a “sign of attempted neuron regrowth after trauma” (Max 49). Gerstmann-Straussler-Scheinker disease is symptomatically as well as molecularly different from both Creutzfeldt-Jakob disease and Fatal Familial Insomnia. Unlike the previous two, which usually have a later onset, the onset of Gerstmann-Straussler-Scheinker disease usually occurs in an individual’s late thirties or forties and has an average duration of seven years, significantly longer than Creutzfeldt-Jakob and Fatal Familial Insomnia (“Gerstmann-Straussler Disease; GSD”). In addition, Gerstmann-Straussler-Scheinker disease is identified by extreme cognitive decline and cerebellar ataxia (“Gerstmann-Straussler Disease; GSD”). Pathologically, Gerstmann-Straussler-Scheinker disease causes large amyloid plaques to form in the cerebrum, cerebellum, and cerebral cortex, not in the thalamus like in Fatal Familial Insomnia (“Gerstmann-Straussler Disease; GSD”). Molecularly, there appears to be a link between P101L mutation and the disease, which has also been proven in mice (“Gerstmann-Straussler Disease; GSD”). Prion diseases, despite being caused by the same protein, remain distinct, symptomatically, pathologically, and molecularly.

Fatal Familial Insomnia is perhaps the most distinct prion disease due to its peculiar symptoms, namely the insomnia, and the part of the brain it attacks. Whereas the prion protein attacks the cerebrum and cerebellum in Creutzfeldt-Jakob disease and

Gerstmann-Straussler-Scheinker disease, the prion protein attacks the thalamus in Fatal Familial Insomnia. Despite a lack of funding for research for a cure for the disease, Dr. William Dement, a Stanford professor, believes that more funding should be given in hopes that discoveries in the disease can also help to cure, alleviate, or more effectively medicate the more normal insomnia that millions worldwide experience (Max 246).

Unlike Creutzfeldt-Jakob disease, there are not many cases of sporadic infection; Fatal Familial Insomnia, as its name implies, is largely genetic. As a result, it causes little threat to public health, as Mad Cow Disease once did and remains to do so, should a large outbreak occur. In general, considerable funding should be given to prion disease research, as it may provide clues to the understanding and perhaps eventual cure of other currently incurable and mysterious diseases, such as Alzheimer's, Huntington's, Lou Gehrig's and other protein-related diseases (Max xxiii). Pruisner, who won the Nobel Prize for the discovery of the prion protein, claimed he would have a cure in five years (Max xiv). That was 1998. So far, a cure for prion disease and other protein-related diseases has remained elusive.

Works Cited

- "Creutzfeldt-Jakob Disease; CJD." Online Mendelian Inheritance in Man (OMIM). 30
November 2009 <<http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=123400>>
- "Fatal Familial Insomnia; FFI." Online Mendelian Inheritance in Man (OMIM). 30
November 2009 <<http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=600072>>
- "Gerstmann-Straussler Disease; GSD." Online Mendelian Inheritance in Man (OMIM).
30 November 2009 <http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=137440>
- Max, D.T. The Family That Couldn't Sleep. New York: Random House, 2006. Print.