Fatal Familial Insomnia

A Summary of Its Nature and the Major Studies

Eric Schools

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Honors Program of Liberty University.

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Randall Hubbard, Ph.D.
Thesis Chair

_____

Norman Reichenbach, Ph.D.
Committee Member

_____

Andrea Beam, Ed.D.
Committee Member

_____

Brenda Ayres, Ph.D.
Honors Director

_____

Date

Abstract

Fatal Familial Insomnia (FFI) is an insidious prion disorder that tends to manifest itself as

a patient reaches middle age following a pattern consistent with autosomal dominance. A

wide range of symptoms are represented, many related to motor function and autonomic

regulation, but degeneration of certain areas of the thalamus is present in every case.

Genetically, the condition is transmitted only within families, but it has been

demonstrated by Jackson et al. (2009) that FFI can be transmitted by exposure

to/ingestion of infected material. A number of groundbreaking studies are discussed.

These include the initial documentation of FFI as a prion disorder by Medori et al.

(1992), the identification of codon 129 on PRNP as a locus for prion disease

susceptibility by Palmer et al. (1991), the discovery that the aberrant isoform PrP^{sc}

requires the normal PrP protein in order to produce infectivity by Mallucci et al. (2003),

and others. There are no effective treatments for FFI as of yet; scientists are still

searching for all the pieces to the puzzle.

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Introduction

Fatal familial insomnia (FFI) is one of the more horrifying illnesses one may contract, but it is also one of the least known. It has been termed "familial" because it is passed down genetically within very few families worldwide and fatal because it inevitably causes the unfortunate victim's demise (Gistau, Pintor, Matrai, & Saiz, 2006). Its pattern of occurrence within families shows that it propagates following the principle of autosomal dominance; that is, a person with the condition has a 50% chance of passing the trait in question on to the offspring regardless of the offspring's gender. Some believe that the very first instance of the mutation for FFI was an Italian physician who passed the "curse" on to his family before his death in 1765 (Schadler and Viddy, 2008).

FFI is a prion disease which refers to the fact that its underlying cause is actually prions or "altered isoform[s] of a protein that become resistant to treatment with proteases" (Medori et al., 1992). The name prion is actually derived from the fact that the mutated proteins are protease-resistant (PrP) (Medori et al., 1992). Prions were originally thought to be "proteinaceous infectious particles"; however, more recent studies have shown that they are actually protease resistant proteins that were somehow misfolded (Jackson et al., 2009, p. 438). The proteins alone can still produce prion infection if they are introduced into a host as demonstrated by Jackson et al. by injecting healthy mice with a brain homogenate taken from FFI-infected mice. Their findings and the implications, thereof, will be discussed in greater detail later. Prions are currently defined as

infectious proteins that are abnormal forms of normal cellular proteins,

that proliferate by inducing the normal protein to convert to the abnormal

form, and that in mammals include pathogenic forms which arise

sporadically, as a result of genetic mutation, or by transmission (as by

ingestion of infected tissue and which upon accumulation in the brain

cause a prion disease. ("prion," 2007).

The lethal nature of prion diseases in general and specifically FFI is quite well-documented. However, in FFI patients, the precise cause of death is still somewhat nebulous (Scheinken & Montagna, 2006). Some FFI patients have not shown enough neural damage postmortem to point to it as the cause of death. Some insomnia studies using rats have noted degeneration in the supraoptic nuclei (SON) in the anterior portion of the hypothalamus, which is involved in the regulation of many homeostatic operations. It has been posited that, if the proper function of this area of the hypothalamus is adversely affected, it could explain some of FFI's symptoms (Scheinker & Montagna, 2006).

Discovery

FFI was first documented in 1986. Since then there have been a total of twenty-two families reported to suffer from this "curse" (Harder et al., 2004). The initial documentation resulted from the study of two similar cases within a particular family in 1986; twenty-nine cases were subsequently confirmed within that family in a study conducted by Medori et al. (1992). The fairly wide variation of symptoms centering upon the apparently untreatable insomnia suggested that the condition might be propagated by prions. Scientists confirmed this hypothesis by running analyses upon tissues from

patients suffering from FFI and Creutzfeldt-Jakob disease as well as some other family members and non-family subjects who were not afflicted with any such disease. The analyses indicated that FFI is in fact a prion disease that comes about through a point mutation at codon 178 of the prion protein. At this location on the gene, aspartic acid is replaced with asparagine which produces the FFI phenotype, but only in some cases. It was noted in this same study that all four of the members who were FFI-symptomatic tested positive for the codon 178 point mutation, but there were also eleven test subjects in which the mutation was found who were asymptomatic and well past the median age of onset, which "indicates that the penetrance of fatal familial insomnia is incomplete" (p. 447). The discovery of other determinant factors of the FFI phenotype is a topic that will be discussed later in the paper. It was also in these studies that the autosomal dominant nature of the disease was discovered (Medori et al., 1992).

The purpose of this paper is to provide a literature review of some of the major studies that have been conducted on FFI and issues closely related to it. For the sake of simplicity, the studies and their findings will generally be presented in chronological order. The discussion of the aforementioned items will commence after the initial discussion upon the nature of prions themselves and the relationships between the diseases they cause.

Prions
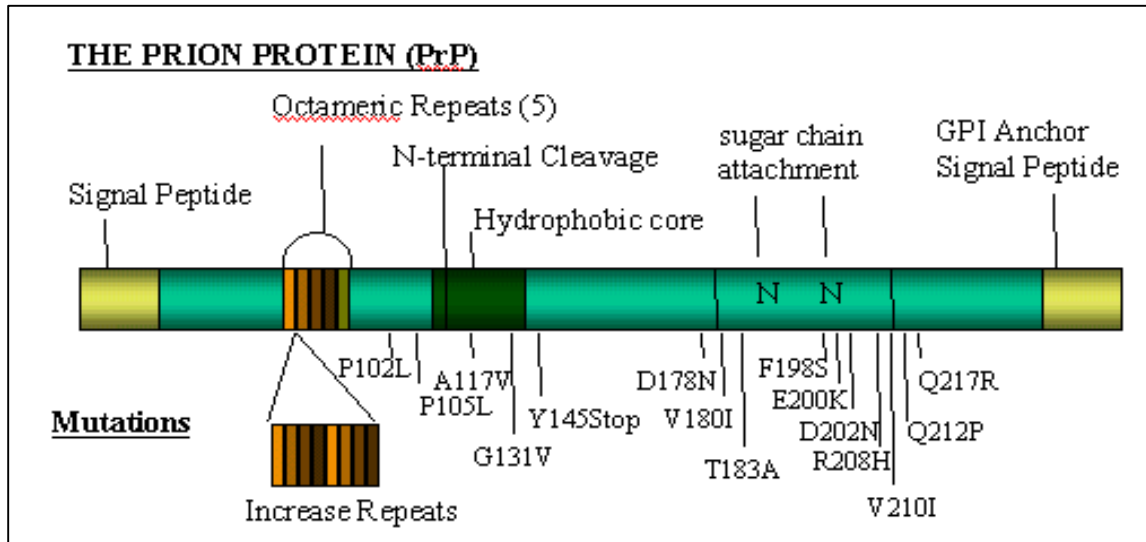
Figure 1 The physiological features (upper labels) and the identified mutations (lower labels) in the prion protein (PrP). The abnormally augmented number of octameric repeats is known as octameric peptide repeat insertion (OPRI).

As previously stated, FFI is actually propagated by proteins referred to as prions because of their resistance to the enzyme protease (Medori et al., 1992). Specifically, prions are aberrant isoforms of a protein called PrP which is coded for by the gene PRNP (Mead, 2006). Prions were first discovered in 1982 by Stanley Prusiner (Pettersson, 1997). The proper function of the PrP is theorized to be to maintain stability in Schwann cells (Frankel-Couzin, 2010). However, a misfolding of PrP can cause any one of several prion disorders: Creutzfeld-Jakob, kuru, fatal familial insomnia, and Gerstmann-Straussler-Scheinker syndrome (GSS). There is considerable overlap in the range of symptoms with which each of these conditions presents, so, for the sake of accuracy, a genetic diagnosis is required. One of the ways in which these disorders may be propagated is by genetic inheritance of the mutation; this method of contraction accounts for roughly 10-15% of all the cases of prion disorders and is heavily suggested in the name of the disease with which this paper deals. The research on the demographic

representations of prion disease is far from complete, but according to a review of several

studies, the most common PrP mutations found were P102L, E200K, D178N, and OPRI

(Mead, 2006). Octapeptide repeat insertion (OPRI), an aptly termed condition, causes

isoforms of the prion protein to arise due to too many octapeptide repeats being inserted

at the repeat region (Figure 1) (Capellari et al., 2011). OPRI tends to produce extremely

varied symptoms which may include cortical dementia (cognitive deficiencies resulting

from negative effects on the cerebral cortex), spasmodic movements, motor symptoms,

and myoclonus (muscular jerks) (Mead, 2006). The P102L mutation produces the GSS

phenotype, the primary symptoms of which are "a slowly progressive ataxia with later

dementia" (p. 277). The E200K mutation normally produced symptoms that are nearly

identical to the sporadic form of Creutzfeldt-Jakob disease: accelerated dementia

accompanied by spasms and motor dysfunctions (Mead, 2006). The D178N mutation is

the one that will be focused upon most closely since it is the mutation that has been

strongly linked with the FFI phenotype (Medori et al., 1992).

One of the more insidious features of prions is that they can infect an organism

with proteinaceous material alone. A misfolded protein may be inherited genetically, but

it may also be transmitted to humans by a vector such as a cow infected with Bovine

Spongiform Encephalopathy (BSE) which is a "new phenotype of acquired prion disease,

variant Creutzfeldt-Jakob disease (vCJD)" (Mead, 2006, p. 274). This disease was first

described in England and is a prime example of the way in which a prion disease may be

transmitted simply by proteins – even between species (Schonberger, Belay, & Sejvar,

2010). A correlation between the presence of BSE in cows and vCJD in humans was first

drawn in 1996; the vector of the disease was beef that contained the pathogenic isoforms

of the prion protein (Schonberger et al., 2010). This case has great socio-political resonance because it created quite a scare in the late 1990s and early 2000s. Between the years of 1995 and 2006, 195 cases of vCJD were reported; most occurred in England (165), but there were two in the United States (Schonberger et al., 2010).

As previously mentioned, the point mutation (G→A) that typically produces FFI occurs at codon D178N; however, it is interesting to note that in a more recent study, of the nine patients presenting with the specific insomnia that is characteristic of the condition, "4/9 had sporadic CJD, 1/9 had a V210I mutation, but none had D178N" (Mead, 2006, p. 278). Because of the fact that all prion disorders are so closely related, being mutations on the same protein, there is a significant overlap of the typifying symptoms. There exists data that indicates that some prion disorders may be even more closely related than scientists originally believed. This topic will be covered in greater detail later.

Another concern within prion research is any additional factors that would make one more vulnerable to prion disease. These susceptibility factors correlate positively with the positive diagnosis of a prion disorder (Mead, 2006). The main susceptibility factor that has been documented is the polymorphism at codon 129 of the prion protein in which either methionine or valine may be present. The key factor seems to be whether or not a particular patient is homozygous for one amino acid or the other; heterozygosity at codon 129 seems to guard the patient against prion infectivity. Another notable polymorphism that has been shown to influence prion disease susceptibility is that at codon 219 between glutamine and lysine (Mead, 2006).

Initial Studies

One of the first studies that described FFI in detail was conducted by Medori et al. (1992) as a follow-up their initial documentation and description of the illness in 1986. The subjects of the 1986 case study presented with insomnia, dysautonomia (dysregulation of the autonomic nervous system) and, most notably, degradation of the cellular nuclei in certain regions of the thalamus (Medori et al., 1992). Further studies within the same lineage produced a much wider range of symptoms including dysautonomia, increasingly severe insomnia, elevated levels of cortisol, reduced production of corticotropin, muscular spasms, deterioration of motor control, hallucinations (in the latter phases), dysarthria (inability to speak clearly), and "impairment of the autonomic, endocrine, and motor systems" (p. 444). One particularly curious symptom was that the patients' memory skills and ability to concentrate for any length of time progressively degraded though they still remained capable of higher thought processes. However, the single symptom common to all of those afflicted was the degradation of the anterolateral and mediodorsal thalamic nuclei (Figure 2) which has become a fairly conclusive indicator of FFI (Medori et al., 1992).

The 1992 study was conducted for the purpose of discovering whether or not FFI was, as the previous research suggested, a prion disorder. The study was conducted postmortem on several generations of a family from northern Italy. The specific procedures included a Dot Blot and a Western Blot, which were conducted in order to test for the presence of protease-resistant prion protein, as well as a specific examination of the PrP gene PRNP which were conducted on two people who had been diagnosed with

FFI, three Creutzfeldt-Jakob disease patients, and a control group of six people with no

aberrant features (Medori et al., 1992).
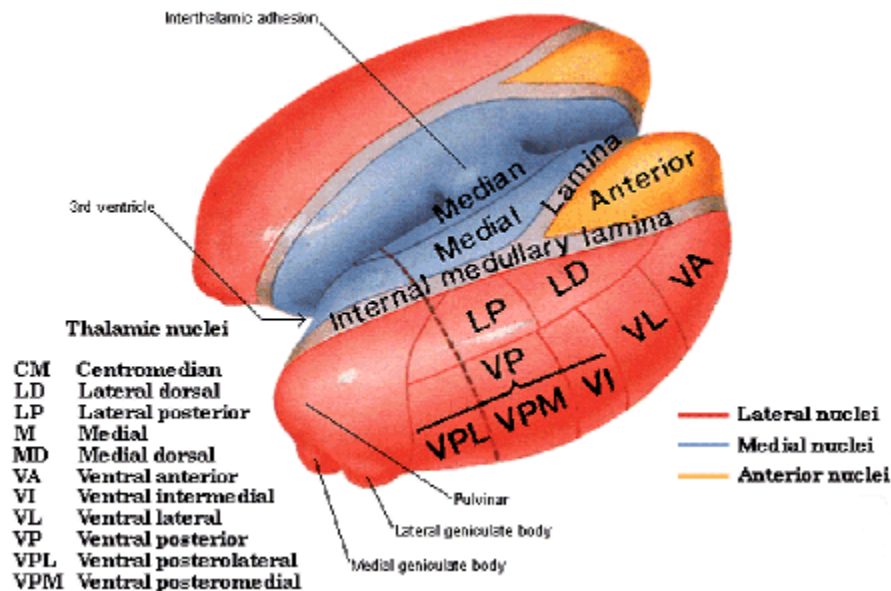
Figure 2 A diagram of the thalamus which highlights its specific regions. The regions primarily affected by FFI are the lower (ventral) portion of the anterior region and the upper (dorsal) areas of the medial region. Studies have shown that the degradation in the mediodorsal region is the primary reason for the loss of sleep spindles (Lugaresi et al., 1998). Figure modified from "Clinical features" (2011).

Both the dot blot and the western blot analyses indicated the presence of protease-

resistant PrP in the brain tissue of both of the FFI patients and the Creutzfeldt-Jakob

patients but not in any of the control subjects (Medori et al., 1992). However, the results

produced by the western blot show that though there is some overlap, the size of the

particles found in the Creutzfeldt-Jakob patients differ from those found in the FFI

patients, which led the researchers to speculate "that they derive from different abnormal

isoforms of PrP" (p. 446). Additionally, the dot blot analysis yielded results positive for

protease resistant PrP in the basal ganglia, cerebellum, parietal lobe, temporal lobe, and

frontal lobe (Medori et al., 1992). These observations may account for the wide variety of

symptoms with which FFI presents.

Analysis of the PrP gene "demonstrated heterozygosity of the GAC → AAC mutation in codon 178 of the PrP coding region that results in the substitution of asparagine for aspartic acid" (Medori et al., 1992, p. 446). It was found that this mutation was closely connected with FFI. Curiously, Medori et al. also discovered that this point mutation was present in many members of the family who had never presented with the FFI phenotype and were well past the median age of onset (at the time) of 49, which indicates that, in addition to being autosomally dominant, the mutation also demonstrates incomplete penetrance.

Effects on Sleep Spindles
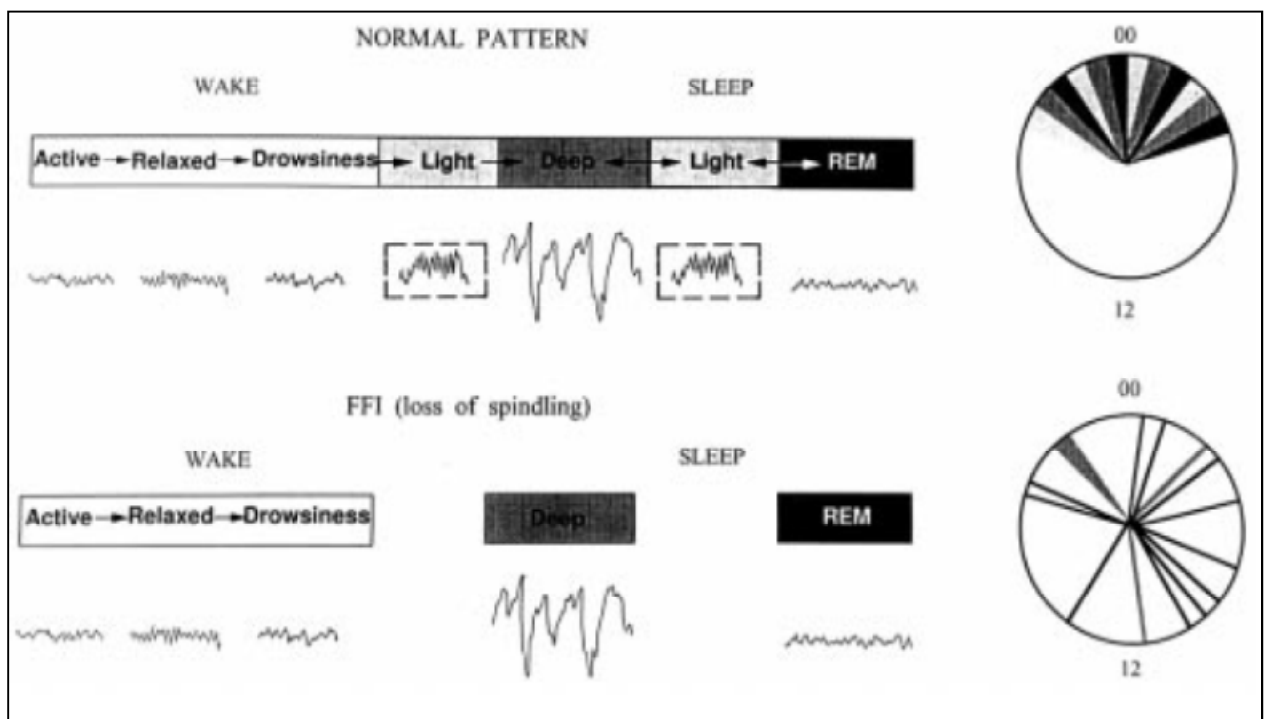
 Figure 2 "The upper panel shows the normal sequence of initiating and maintaining sleep, and the cyclic passage from light to deep and REM sleep stages, as shown in the EEG tracings below and in the 24-hour wake-sleep organization (to the right). The lower panel shows how loss of spindling in FFI makes the normal transition from wake to deep and from deep to REM sleep impossible, disrupting the 24-hour wake-sleep cycle (to the right)" (Lugaresi et al., 1998, p. 522).

Sleep cycles usually proceed in a manner similar to that shown in the upper portion of Figure 2 with a typical sleep cycle lasting about 90 minutes, though the proportions of the different types of sleep will vary depending on the time (Smith, Robinson, & Segal, 2011). A normal adult getting the appropriate amount of sleep (7.5-9 hours) will go through 5-6 complete cycles of sleep per night. These sleep cycles are crucial for restoring and repairing the body (deep sleep) and restoring the mind, memory and immune system (REM sleep) (Smith et al., 2011).

According to EEG data, the sleep spindles, which are the EEG manifestations associated with 'light' sleep, fail to form in FFI patients (Lugaresi et al., 1998). Sleep spindles are actually initiated through the function of the reticular thalamic nuclei; however, the mediodorsal thalamus is integrally involved in conducting the signal to the prefrontal cortex. Thus, the progressive destruction of the mediodorsal thalamus renders the unfortunate patient unable to conduct the signals that would allow him to form a sleep spindle which negates the possibility of attaining slow-wave (deep) and REM sleep via the normal pathways (this concept is illustrated in Figure 4). Additionally, many of the other symptoms of FFI tend toward sending the bodies systems into a state of heightened sensory perception, which may also produce a negative impact on circadian rhythms. The differences between EEGs of normal and FFI subjects may be found in Figure 3. Occasionally, FFI patients will exhibit brief, atypical lapses into REM or slow-wave sleep; the exact duration of these short spells of somnolence is unspecified (Lugaresi et al., 1998).
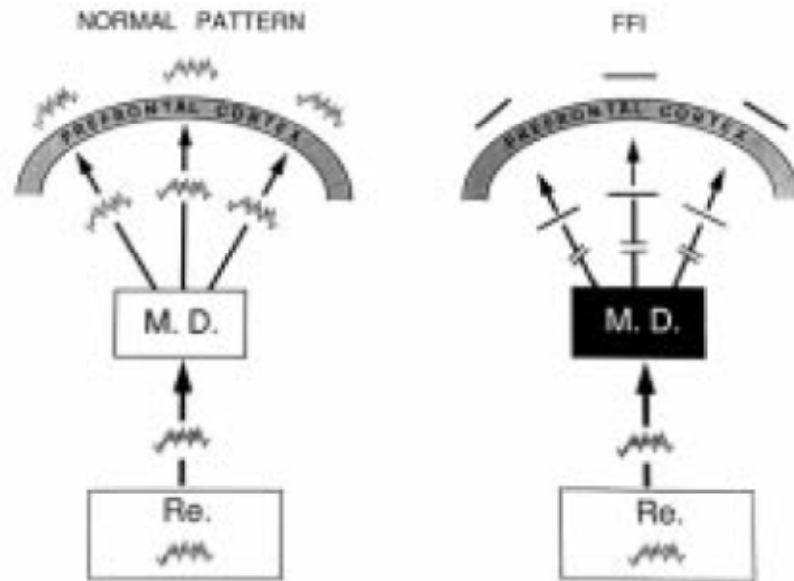
Figure 4 "Left: schematic representation of the transmission of spindling from the reticular nucleus for the prefrontal cortex through mediodorsal nuclei. Right: Atrophy of the mediodorsal nuclei prevents transmission of spindling." (Lugaresi et al., 1992)

Somnolent FFI Effects

One of the premier sleep studies performed on an FFI patient was conducted by Tinuper et al. (1989). The results of the study served to reinforce the key role that the thalamus plays in the regulation and control of sleep cycles. It was found that drugs that normally induce sleep, in this case benzodiazepine and barbiturates, had no effect on the FFI patient. The patient's EEG readout showed erratic activity, particularly in the areas of oro-nasal, abdominal, and thoracic respiration; this allowed the researchers to quantitatively documented a number of physiological symptoms of fatal familial insomnia (Figure 3) (Tinuper et al., 1989). Some of these symptoms included the aforementioned aberrant breathing patterns, tachycardia, muscle spasms, and patterns of movement indicating that the patients were pantomiming the content of their dreams (Montagna, 2005).

Another study observed several FFI patients over a number of years in order to

track the progression of their illness (Sforza et al., 1995). In addition to affirming that the

abbreviation and destruction of the normal sleep cycle was a symptom that was present in

all cases of FFI, they also identified and described a key difference between the ways in

which circadian rhythm destruction presented in cases of a short duration versus those of

a longer duration. Specifically they observed that the elimination of the deep sleep phase

and reduction of the REM sleep phase were present in short-duration patients, whose

period of illness was less than one year, and absent in long-duration patients, whose

period of illness was greater than two years (Sforza et al., 1995).
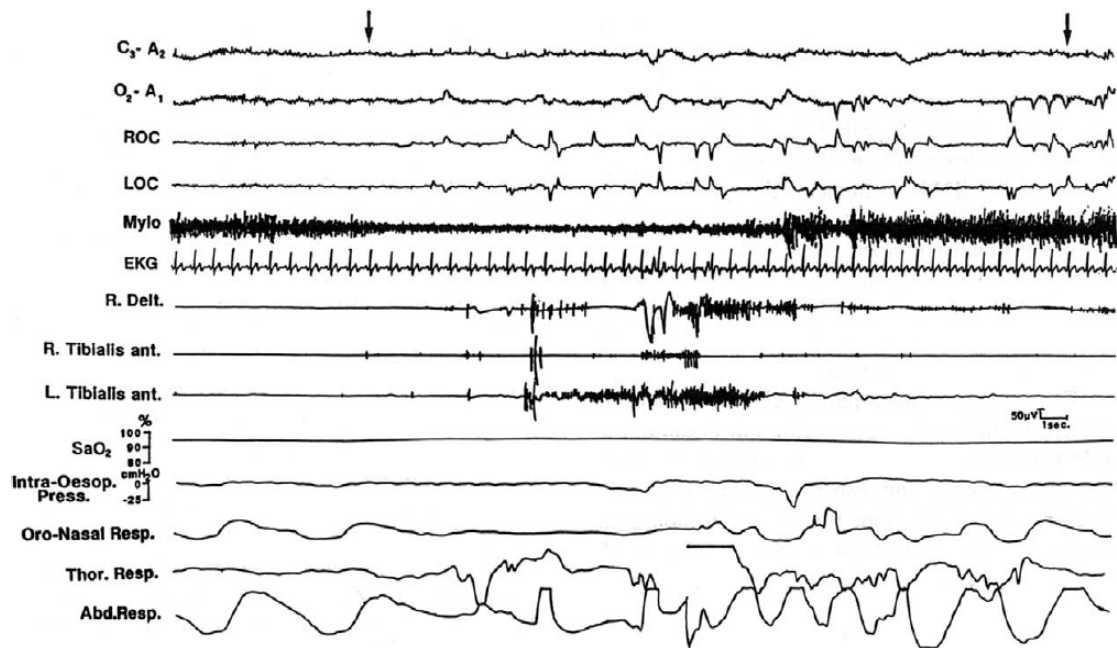
Figure 5 "Polygraphic recordings of an enacted dream episode (between arrows) in a FFI
patient, showing EEG fast activity of REM sleep, REMs (ROC and LOC) with irregular
chin muscle atonia (mylo) and jerks in the limb muscles." (Montagna, 2005)

Figure 5 is the first EEG readout from an FFI patient from the study conducted by

Tinuper et al. (1989). Montagna (2005) interprets this data as:

EEG tracings [alternating] between two states, one of diffuse alpha activity with

normal antigravitary tone and normal responses to presented auditory bursts,

corresponding to a behavioural state of wakefulness; the other of desynchronized

EEG activity with numerous REMs, tachycardia, and irregular breathing, brief or

rudimentary atonia on antigravitary muscles and frequent irregular jerks

interspersed with more complex motor activity of the limbs, ad unresponsiveness

to presented auditory bursts.… (p. 342)

These two vastly different regions of the EEG readout indicate the different states

of consciousness that exist within an FFI patient; one representing normal consciousness,

and the other representing a sleep-like state in which the actions performed in dreams

manifest in reality (Montagna, 2005). Because of the way in which the patients indicate

that they dreamed and were observed acting out activities in their sleep-like state, this

state was termed an "oneiric stupor" (p. 342). Normal sleep patterns were not attained

even with the use of pharmaceutical aids. Another differentiation was also noted between

those whose illness progressed rapidly and those whose illness progressed more slowly;

rapidly-progressing patients produced no slow-wave sleep indicators on the EEG, though

they did experience brief lapses into aberrant REM sleep during wakefulness, whereas

the slowly-progressing patients showed both slow-wave sleep and REM sleep which both

tapered off as their malady progressed. Basically, the short duration patients tend to

experience a severe reduction in sleep time and spindle formation, whereas long duration

patients tend to show these symptoms more gradually (Montagna, 2005).

Melatonin and FFI

Another group investigated the relationship between melatonin levels and

disruption of circadian rhythms in FFI patients. They monitored the melatonin levels and

the rapid eye movement events of two subjects diagnosed with FFI and six control

subjects. Their investigation yielded an inverse correlation between melatonin levels and

the regularity of circadian rhythms in FFI patients; as the melatonin levels decreased, the

circadian rhythms became more erratic (Portaluppi et al., 1994). The issue with these

findings is that it is not apparent whether the decreased melatonin affected the circadian

rhythms or vice versa (Portaluppi et al., 1994). There have apparently been no studies

conducted on the viability of supplemental melatonin as a treatment option for FFI.

Austrian Family

A study conducted by Almer et al. (1999) paints an even bleaker picture of FFI.

This study was conducted on five members of the first identified Austrian FFI family:

two brothers, their mother, their second cousin, and her mother. The family as a whole

contained 13 members in whom the FFI phenotype was identified either by genetic

testing or by previously existing records. In addition to the symptoms mentioned

previously, the test subjects in this study also presented with apathy, double vision,

constipation, and extreme weight loss to the point of emaciation. Also, three out of the

four patients studied did not present with the major, progressive sleep disturbances for

which FFI is named, though some had seemingly isolated sleep disturbances; however,

most tended to show signs of autonomic dysregulation, myoclonus, and ataxia (Almer et

al., 1999).

Studies conducted on brain tissue from the four patients yielded interesting

results. As expected in cases of FFI, the thalamus showed considerably more evidence of

degeneration than other areas of the patients' brains, though protease-resistant PrP

plaques were found in other brain regions including both grey and white matter (Almer et

al., 1999). These findings support those made by Medori et al. (1992) in that degeneration

occurs in multiple areas of the brain in FFI patients; specifically, atrophy and degradation

were noted in the "inferior olivary nuclei… dorsal raphes and superior central nuclei, in hypothalamus, some brainstem nuclei and spinal grey matter" (p. 9-10).

This study also contained an amplification and analysis of the gene PRNP similar to the one conducted by Medori et al. (Almer et al., 1999). The results corroborated those obtained by Medori et al. and they also noted that every subject was homozygous for methionine at codon 129 of PrP, which is one of the primary determinants for FFI. The presence of the aspartic acid to asparagine mutation at codon 178 of PrP that, until recently, had been proof-positive of FFI was also noted in this study (Almer et al., 1999).

Chinese Family

The first documentation of a Chinese family afflicted with FFI came about in 2004 through the efforts of Spacey et al. (2004). The initial subject, a 36-year-old male, became symptomatic after he relocated to Canada. He began to present with classic FFI symptoms including insomnia, myoclonus, episodes of apnea, hypophonia, general ataxia, and others; most notably, weight loss and the development of hypersomnia in the later stages of his illness. Twelve months after the onset of symptoms, he died due to pneumonia. The patient's aunt on his father's side was the second patient; her symptoms were slightly different than her nephew's and included "myoclonic jerks in all of her limbs" (p. 124). Genotypically, the man was homozygous for methionine at codon 129, which is a susceptibility factor for FFI. Under this assumption, it is incredibly unlikely that anyone of Chinese ancestry would ever acquire CJD genetically because statistics show that, in members of this ethnicity, the occurrence of heterozygous valine at codon 129 is only 3%, and the occurrence of homozygous valine is 0%; therefore, FFI is indicated in Chinese families with a history of prion-related illnesses. One important

conclusion that Spacey et al. reached was that, in addition to much pathological activity

in the thalamus, some FFI symptoms can be attributed to the improper functioning of the

brain stem, which might explain the dysregulation of the autonomic processes. These

findings certainly warrant further investigation.

Another study involving Chinese FFI patients was conducted in 2010 in the

Henan Province of China. It began with a 48-year-old man who reported sleep

disturbances and abnormalities and dysautonomia; his niece was experiencing similar

symptoms, so they were both hospitalized until tests could be conducted (Shi et al.,

2010). While under observation, the man experienced, in addition to the aforementioned

symptoms, extreme weight loss, an elevated heartbeat and blood pressure, an apparent

itching sensation that cause him to scratch, tug, and tear his clothing, apathy,

disequilibrium, ataxia, and other symptoms; his niece experienced comparable symptoms

with the addition of apparent hallucinations. Aside from the aforementioned symptoms

which are obviously quite serious, the diagnostic tests yielded surprisingly mild results:

his EEG showed slight slowing, which is nothing like the deterioration noted in Figure 4,

and his MRI showed no evidence of an aberrant condition, yet he still died fairly soon

after being discharged from the hospital.

Within the extended family, it came to light that, out of the 135 family members

who were examined, either directly or indirectly, there were eleven suspected cases of

neurodegenerative disease within the most recent three generations, though "except for

Case 2 [the man's 26-year-old niece], none of family members in the next or following

generations have neurological symptoms to date" (Shi et al., 2010, p. 294).

Both cases of FFI in this study were found, by means of gene amplification, to

possess the aspartic acid to asparagine mutation at codon 178 and the homozygosity for

methionine at codon 129 of PRNP – the genotype that produces FFI (Shi et al., 2010).

Analyses were conducted on blood samples taken from the two FFI patients and from

thirty of their relatives. The results showed that nine of those tested were positive for the

codon 178 mutation; it is notable that the eldest one to have the mutation is 53 years of

age and has not yet become symptomatic. At the end of their paper, the researchers note

that the marked differences in the age of onset of FFI likely indicate an additional

determinant of the disease's pathology (Shi et al., 2010).

Phenotypic Variability

Phenotypic variability is an interesting and perplexing feature of FFI. The illness

does not always present with the same symptoms, and it is not conclusively identifiable

without conducting genetic analyses – at least that was the case. Zarranz et al. (2005)

conducted a study into the unusually high occurrence of prion disease in the Basque

region of Spain; of a regional population of 2.1 million there were 23 genetically

confirmed cases of prion disease in the ten-year period from 1993-2003. Prion diseases

simply do not occur with this high of a frequency unless some extenuating circumstance

is afoot. Zarranz et al. speculate that the reason for such a large percentage

(comparatively) of prion disease is related to a founder effect since a significant portion

of the patients that were evaluated in this study were related to one another by blood.

The most significant feature of this study is that its results question the well-

established view that both familial Creutzfeldt-Jakob disease (CJD) and FFI arise as a

result of mutations on PrP at codons 178 and 129 (Zarranz et al., 2005). Codon 129 is the

determining factor in that if it codes for methionine, FFI will result, whereas if it codes

for valine, CJD will be the phenotype. This study noted ten cases in which the both

mutations were present and codon 129 was homozygous for methionine, yet CJD was the

result. This data led the researchers to conclude that "[t]he considerable clinical and

pathological overlapping observed even among homozygous 129MM patients favours the

view the FFI and CJD178 are the extremes of a spectrum rather than two discrete and

separate entities" (p. 1495). These genotypical data are in Table 1 below. This conclusion

is not altogether surprising because both mutations are on the same gene. Multiple

mutations leading to the same condition is not uncommon in other genetic illnesses such

as Wilson's disease.

Table 1

Table 4	Influence of the polymorphism in codon 129 over the phenotype in carriers of the D178N mutation				
Genotype polymorphism, codon 129	Number of patients	Phenotype	Number of patients	Mean age at onset, years (range)	Mean duration of illness, months (range)
VV	0	–	–	–	–
MV	6	CJD	4	52.5 (38–71)	19 (2–40)
		FFI	2	52 (50–54)	17 (15–19)
MM	17	CJD	7	56.5 (38–69)	14.8 (10–20)
		FFI	10	63.2 (37–76)	10.8 (6–18)

Seven of the homozygous 129MM patients had a CJD phenotype instead of a FFI phenotype. The differences in age at onset or duration of illness did not reach statistical significance.

This table shows the numbers of CJD and FFI cases as they relate to the genotypes at codon 129 (Zarranz et al., 2005)

Early Age of Onset

We have seen that there is considerable overlap between the phenotypes and even

the genotypes of prion diseases, particularly CJD and FFI. Now we shall discuss a

particular case of two FFI patients whose age of onset was surprisingly low. Harder et al.

(2004) calculated from observed cases the median age of onset of FFI symptoms to be

49.5 years of age. However, there have been seven cases of patients developing

symptoms and subsequently succumbing to the illness prior to the age of 30, which is the

age range during which Creutzfeldt-Jakob patients generally become symptomatic

(Harder et al., 2004). These findings would seem to reinforce the idea that CJD and FFI are simply very extreme phenotypes of the same condition.

The cases that Harder et al. (2004) examined were those of two members of a German pedigree in Saxony with a high incidence of familial prion disease; in this case, the malady was FFI. The atypically high FFI occurrence is suspected to be the result of a founder effect similar to the one documented in the Basque region of Spain. In any case, the two patients in question became symptomatic at ages 23 and 24 – well below the mean age of onset (Harder et al., 2004).

Both cases presented with similar symptoms, all typical of FFI: insomnia, ataxia, dementia, dysautonomia, hallucinations, loss of motor function, and other symptoms. Both patients eventually died of pneumonia. This seemingly peculiar cause of death was likely because of the severely inhibited immune system that lack of REM sleep produces. It is also noteworthy that both patients were shown to be homozygous for methionine at codon 129 of the PRNP and they also had the D178N mutation on the same gene – the genetic markers of FFI (Harder et al., 2004).

One tool that is useful for mapping the localities of PrP isoforms in the brain is positron emission tomography (PET) which produces an image that appears similar to that of an MRI (Harder et al., 2004). As represented by the Figure 6, PET showed a decrease in glucose metabolism in the thalamic region; this is a strong indicator of thalamic degeneration and consequently, FFI. Harder et al. believe that many cases of early onset FFI are not diagnosed as they should be because "the clinical and neuropathological diagnosis of rapidly progressive FFI is often difficult to establish" (p. 721). They also observed that females who have become FFI-symptomatic tend to

survive for a longer period of time than the males, and they speculate that males might be more susceptible to early age of onset FFI than females, though there is not currently enough data to make such a claim with any degree of certainty (Harder et al., 2004).
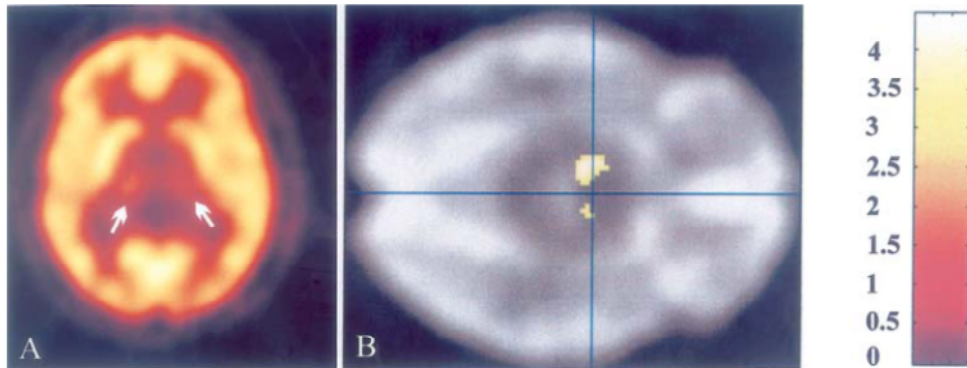
Figure 6 "Original PET (A) and SPM (B) showed reduced glucose metabolism in both thalami pronounced on the left side." (Harder et al., 2004)

Methods of Transmission

As is fairly obvious at this point, one of the most common methods of transmission of the protein isoform that produces FFI is one's heredity; this trait manifests itself following the pattern of autosomal dominance, which differs from most other inherited diseases (Shi et al., 2010). The hereditary propagation of FFI has been discussed in a fair amount of detail, so let us turn our attention to another means of transmission.

Jackson et al. (2009) conducted an experiment to test, in a controlled environment, whether or not prions could really infect another host simply by being transferred to that host. The test was conducted using knock-in mice that had two of their genes altered so the scientists could conclusively determine the origin of infective material based on its response to the 3F4 antibody which recognizes human PrP. FFI was used for this test of prion infectivity because its battery of symptoms is so distinctive among prion disorders that it would be much less likely to be mistaken for some other

malady. The experiment was a success in that, simply by substituting the appropriate

amino acid in the proper mouse analog of codon 178 of PrP, the researchers produced

mice that eventually demonstrated the symptoms commonly associated with FFI; thus

proving that FFI, and other prion diseases, can be transmitted without the need for any

genetic material. In their words, "in the context of an otherwise normal animal, a familial

mutation in PrP is sufficient to cause the de novo appearance of a transmissible agent for

neurodegeneration" (p. 446). Their hypothesis was supported by their data. Brain tissue

from the infected mice was injected into the skulls of Tga20 mice, which are

characterized by having high levels of PrP. This produced symptoms similar to many

prion disorders, but different from the symptoms that the FFI mice experienced (Jackson

et al., 2009).

Advanced Detection

Many diagnoses of FFI and other prion disorders require gene sequencing or other

complicated measures. One group of researchers decided to test whether or not it would

be possible to use magnetic resonance imaging to detect thalamic lesions for the purpose

of diagnosis which would allow the patient to receive treatment in a timelier manner

(Haik et al., 2008). The measuring tool the group employed was a "multimodality MRI

standardized procedure that aimed to estimate the differential sensitivities of FLAIR

[fluid-attenuated inversion recovery], DWI [(diffusion-weighted imaging)] and magnetic

resonance spectroscopy for the diagnosis of human prion disease" (Haik et al., 2008, p.

545). In addition to testing whether or not FFI may be diagnosed using these methods, the

researchers were also testing which of the methods was most sensitive and therefore most

suitable. Haik et al. theorized that FFI would prove to be difficult to detect using these

MRI methods because, when compared with CJD of either the sporadic or variant strains,

the lesions and gliosis (increased presence and size of astrocytes) that occur within the

brain are localized and primarily occur in the thalamus (Haik et al., 2008).

The test subject in this study was a 55-year-old man afflicted with FFI (Haik et

al., 2008). His symptoms began with insomnia but eventually came to include ataxia,

fever, hallucinations, myoclonus, and others typical of fatal familial insomnia. The MRI

procedures were performed a mere four days before his death which occurred just six

months after he became symptomatic. This would insure that the MRI techniques to be

employed would have the greatest possible opportunity to produce positive results (Haik

et al., 2008).
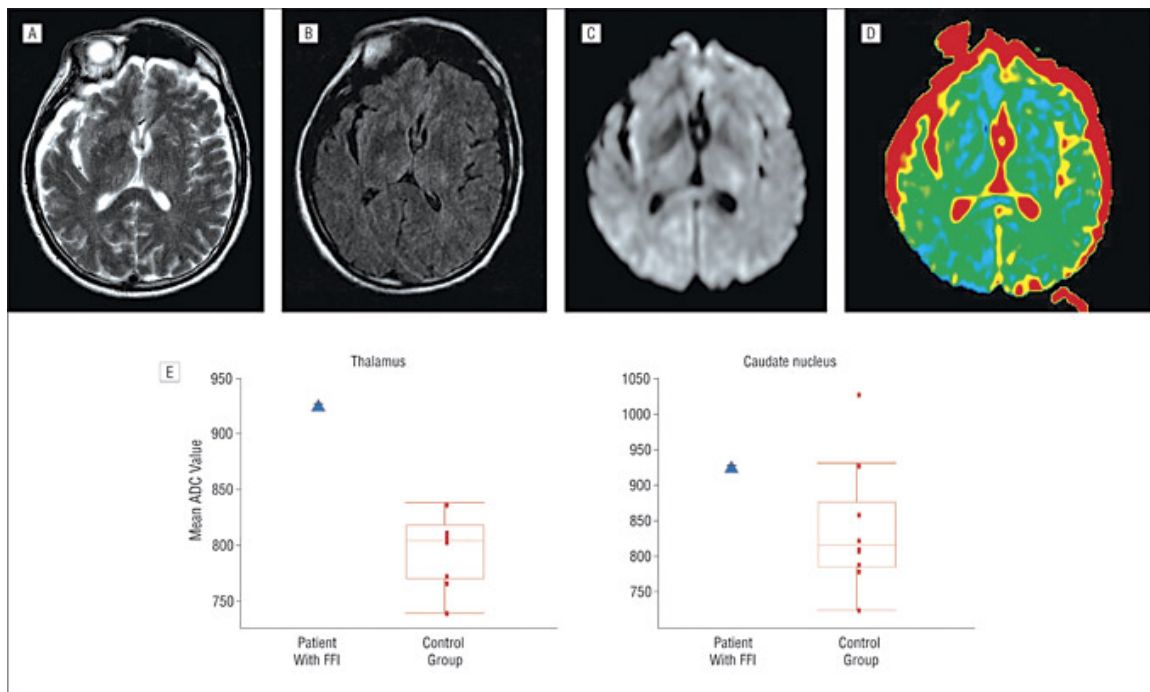
Figure 7 "Magnetic resonance imaging findings in a patient with familial fatal insomnia (FFI) and the D178M mutation (A, T2-weighted imaging sequence; B, fluid-attenuated inversion recovery sequence; C, diffusion-weighted imaging; D, apparent diffusion coefficient of water [ADC] map). Both thalami showed normal signals. E, when compared with the control group, the mean ADC value was increased in the thalamus but not in other regions commonly involved in Creutzfeldt-Jakob disease such as the caudate nucleus." (Haik et al., 2008, p. 546).

In addition to the FFI patient, this study also involved performing the MRI procedures on eleven people for the purpose of establishing a control group (Haik et al., 2008). The results of the T-2 weighted imaging and fluid-attenuated inversion recovery seemed to indicate a normal brain. It was only the diffusion weighted imaging and the resulting apparent diffusion coefficient of water (ADC) map that resulted that indicated gliosis in the thalamic region (Figure 7). After the patient died, the thalamic gliosis indicated by the MRI procedures could be compared with the actual regions of the patient's brain during the autopsy. Atrophy of the thalamus was not apparent to the naked eye; however a microscopic examination showed an incredible amount of gliosis, which was indicated by the ADC map. This study also showed no spongiform morphology at high levels of magnification in the cerebellum, the striatum, or the isocortical regions. Immunostaining for the prion protein yielded no normal PrP; that is, the PrP that was present had been converted to one of its isoforms. Testing for proteinase K-resistant PrP, however, yielded positive results. These findings demonstrate that magnetic resonance imaging can be used to detect the effects of FFI, even in the thalamus (Haik et al., 2008). With some perfecting, this will significantly speed up the prion disease diagnosis process so that patients may receive treatment more promptly.

Treatment

Scientists are currently working to discover viable methods of treating prion disorders. According to Mallucci et al. (2003),

> no treatment has been effective in animals after the onset of clinical signs of the
> disease, and no agent has prevented the disease progression in mice during the

asymptomatic preclinical phase of central nervous system (CNS) scrapie

infection, when intervention would have the greates therapeutic potential (p. 871).

This particular study sought to observe the effects of reducing the amount of PrP

encoded by the host as a means of preventing the host-encoded PrP (PrP^c) from being

subverted to its infectious isoform (PrP^{sc}); this was predicated upon the results of a

previous study that showed that a reduced amount of PrP^c does not adversely affect the

mice that were tested (Mallucci et al., 2003). Mallucci et al. exposed the experimental

mouse group to scrapie about three to four weeks after weaning, but engineered the mice

to remove the PrP^c genes by excision, thus drastically reducing the PrP^c in the organism;

this feat was accomplished through the use of an enzyme called Cre recombinase, which

actually performs the excision, when the mice were about twelve weeks old. The control

group of normal mice infected with scrapie began to show prion disorder symptoms

while the mice in the experimental group did not become symptomatic, but survived for a

much greater length of time (Mallucci et al., 2003).

Mallucci et al. (2003) concluded that the severe reduction of PrP^c did indeed

prevent the mice from becoming clinical prion disease cases, though they were still

infected with scrapie. The removal of PrP^c inhibited the prion replication because it is

essential that PrP^{sc} have host-encoded prion proteins to subvert in order to propagate

itself. They also concluded that the production of PrP^{sc} from PrP^c is not

"[neurotoxic]…because the continued nonneuronal replication and accumulation of PrP^{sc}

throughout the brains of scrapie-infected mice is not pathogenic. Indeed, this may explain

the lack of significant efficacy in vivo of therapeutic agents that reduce PrP^{Sc}

accumulation in vitro" (Mallucci et al., 2003, p. 874). That is to say that the PrP^{Sc} is not

pathogenic in the truest sense of the word.

These findings indicate that suppressing the production and presence of PrP^c would be a possible means of effectively treating prion disorders, perhaps even in humans, before they begin to show symptoms of the illness (Mallucci et al., 2003). These observations, however, are not yet conclusive enough to merit testing on humans. Many FFI-related studies are being conducted using mouse models.

Gene therapy as a possible treatment for FFI is a relatively recent area of study. One such study was conducted by Toupet et al. (2008) using a mouse model of prion disease in order to test the efficacy of using a lentivirus (a retrovirus in which there is a delay between infection and symptom manifestation) in order to deliver The researchers had demonstrated in a prior study that inhibition of prion replication could be achieved by using VSV-G (vesicular stomatitis virus G protein) lentiviral vectors that transported other mutations of PRNP which were dominant and negative. Since prion diseases in humans are not usually diagnosed until symptom onset, Toupet et al. desired to test whether the prion-inhibiting properties of the negative mutant PRNP would have a positive effect in a mouse model. The study was performed upon mice that had shown clearly defined neurological symptoms after being inoculated with a prion strain known as Me7. Lentiviral vectors were made containing the code for the aberrant protein PrPQ167R, which was the mutation that had been shown to inhibit prion synthesis. The mice were treated at either 35 or 105 days after prion infection. The findings of the study indicated that the lives of the treated mice were extended by as much as 20%, improvement was recorded in the are of symptomatic behavior, and decreases in spongiosis and gliosis were also noted. Toupet et al. noted that inhibition was caused by

"competitive interaction between PrPQ167R and PrP^C for PrP^{Sc} "(p. 67). While the study only notes a slowing of the diseases progress, it is a step forward in that it affirms gene therapy as a candidate for further study which could eventually lead to a cure.

Singh, Singh, Das, & Mohan (2010) theorize that the negative effects produced by the presence of PrP^{Sc} (or absence of PrP^C) may come about as a result of an imbalance of redox-active metals that are present in the human body; specifically, iron and copper, since PrP is involved in their metabolism. Irregular amounts of either of these metals can quickly become neurotoxic as a result of oxidative stress – a phenomenon that has been demonstrated in several studies (Singh et al., 2010). Given that oxidative stress plays a significant role in prion disease pathogenesis, Singh et al. posit two methods that may be viable as treatment options for prion diseases: the use of antioxidants to restore oxidative homeostasis within the cells and the use of metal chelators which bind to excess metal ions. While the viability of these methods has been suggested, more testing must be conducted before they may be used to treat humans, particularly in the case of iron because the relationship between excess iron and prion disease is a rather recent discovery (Singh et al., 2010).

Outlook

Scientists are still working to understand the precise effects of the FFI and the specific mechanisms by which it is propagated. A useful development would be to identify the point at which the disease originates and what specific environmental factors lead to its manifestation (Cortelli et al., 2006). Malluci et al. (2003) also mention in their article that it has been suggested that the process of subverting PrP^c to the aberrant isoform produces harmful toxins in the process, which could also be a fruitful study to

undertake. Formulation of an enzyme that inactivates PrP^{Sc} would, in theory, cure the disease, so that would be a course of study worth pursuing. Gene therapy is also a viable option based upon the work of Toupet et al. (2008). People whose parents are afflicted with the disease, like those at risk for Huntington's disease, are often reluctant to get tested for the genetic markers of the illness, even though the genetic markers do not guarantee that the subject will become symptomatic (Schadler & Viddy, 2008). Even as recent as 2009 and 2010, there is still very little that can be done in the way of treatment; even the most promising of current studies show only a lengthening of the disease progression. The vast majority of the papers that have been written on the subject are summaries of experiments to establish patterns of the disease, but FFI is a difficult illness for which to establish patterns. Scientists do not even know conclusively how the altered protein form induces changes in the wild type proteins. While breakthroughs are being made, one article stated the main issue very succinctly: "control and prevention of this disease needs more particular attention" (Shi et al., 2010, p. 297).

While there is still a great deal of progress that must be made before prion diseases can be eliminated or even adequately combated, significant progress has been made in discovering the idiosyncrasies that accompany each mutation on the PRNP gene. In this paper, we have discussed the current understanding of prion diseases, most specifically FFI, and many of the historical and groundbreaking forays into this murky field (summarized in Table 2). Hopefully, breakthroughs in the near future will be able to grace the treatment section with a truly viable option for combating the disease and improving the quality of life of those who are afflicted by it.

Table 2

Author/Year	Accomplishment
Lugaresi et al., 1986	First documented the illness.
Tinuper et al., 1989	Studied the thalamus' role in sleep cycle regulation.
Palmer et al., 1991	Posited that homozygosity at codon 129 of PRNP is a susceptibility factor for prion disease
Medori et al., 1992	Discovered that the critical mutation was at codon 178 of PRNP.
Portaluppi et al., 1994	Noted the correlation between FFI progression and melatonin levels.
Mallucci et al., 2003	Observed that PrP^{Sc} needs PrP^{C} in order to produce more of the altered isoforms.
Harder at al., 2004	Described cases of early onset FFI.
Spacey et al., 2004	First described the illness in a Chinese family.
Haik et al., 2008	Showed that radiological techniques could be used to detect degradation of the thalamus *in vivo*.
Jackson et al., 2009	Demonstrated that prion infectivity could be generated by switching a single amino acid.

The major discoveries in the study of fatal familial insomnia discussed in this paper.

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