Induced Fatal Familial Insomnia: A Genesis Mystery Debunked

Ryan Vlaar*
Department of Biology, Lake Forest College

Summary

The prion hypothesis posits that infectious prions can arise from genes encoding prion-predisposed PrP. This, however, has never exclusively been shown. Research using a knockin approach may provide hard evidence for the genetic origin of human familial prion disease.

Introduction

Prion disease occurs all over the world and across many species, including humans. Prions, or infectious proteins, are transmissible and thought to be generated through infection, sporadically, or genetically.[2,3,5] While there is mounting research in support of the first two means of acquisition, causation of the latter (genetic acquisition) has yet to be definitively demonstrated[6].

Fatal Familial Insomnia (FFI) is a human strain of prion disease that occurs in about 40 families worldwide and is characterized by a loss of slow wave sleep that ultimately leads to death[6]. Due to its familial linkage, FFI serves as the optimum prion strain for studying whether gene mutations can cause the disease, and isolation of this mutation may be used in anticipating the disease before it happens. In an article from the scientific journal Neuron, Jackson *et al*. (2009) knocked in a human mutation associated with FFI and demonstrated the genetic causation of a strain of prion disease.[6] This research has heightened understanding of the genetic mechanisms behind this insidious disease.

The onset of prion disease is correlated with the buildup of protein plaques in neurons that ultimately lead to cell death.[4,5,6] PrP, a protein naturally made in the cell through the DNA pathway, is directly implicated in the buildup of these plaques. Knockout of all PrP proteins in mice shows no acquisition of prions, and therefore PrP must be linked with the disease.[8] The protein-only hypothesis, which is central to understanding the disease, states that the disease is caused when the infectious misfolded form of PrP, called PrPSC, converts normal cellular PrP, or PrPC, into itself and is thus self-perpetuating.[1,3,5,6,8] This information has challenged the central dogma of molecular biology. The PrPSC serves as a template by which PrPC changes-to-fit, and these build up in the cell as they resist digestion by normal cellular mechanisms. Additionally, the idea surrounding the genetic form of the disease is that mutations are thought to cause prions by increasing the likelihood of a misfolding event.[5]

Previous research into the genetic origin of prion disease has come from models using alternative methods of generating the disease.[1,4,6,8] No alternative model fully reflects the human variation of a disease, but criticisms of these previous studies have highlighted the fact that the models used are especially ineffective in translating into humans situations.[6,8] For example, researchers have used transgenic mice expressing both human and mouse PrP to induce the disease and thus cannot discount the possibility of the human strain of the disease arising from confounding interference by mouse PrP.[2] In fact, of all the studies found only one transgenic mouse model that expressed a mutation associated with Gerstmann-Straussler-Syndrome (GSS), which is another strain of prion disease was suggested to cause spontaneous infectivity.[6] Over-expression of the cellular PrP in these models, whether human or mouse, also increases the chance of spontaneous infection occurring in these mice solely due to chance rather than from mutation.[5,6]

A study done by Walker *et al*. was especially relevant because it eliminated these and other confounds by only expressing human PrP in the mouse model. To create a knockin mouse, the human mutation that is thought to cause FFI had to replace the existing mouse PrP gene so that no mouse PrP would be made in addition to the human PrP. Furthermore, in order to show that it was indeed FFI that was generated in the mice and not another form of prion disease, the researchers added a transmission barrier that protected against any pre-existing prions they might be exposed to[6]. By transmitting the disease, the researchers would show that the disease acquired by the mice was, in fact, prion disease.[6]

The results of the study show that the mice with the FFI knockin mutation developed symptoms and exhibited a pathology that was extremely comparable to FFI in humans and was also very distinct from other prion strains. The pathology of FFI in humans shows the most damage in the thalamic region of the brain, which is implicated in sleep patterns[6]. Similarly, the mice exhibited behavioral abnormalities such as loss of normal sleep patterns and brain pathology characteristics that were reminiscent of FFI. This brain pathology showed similar localized damage to the

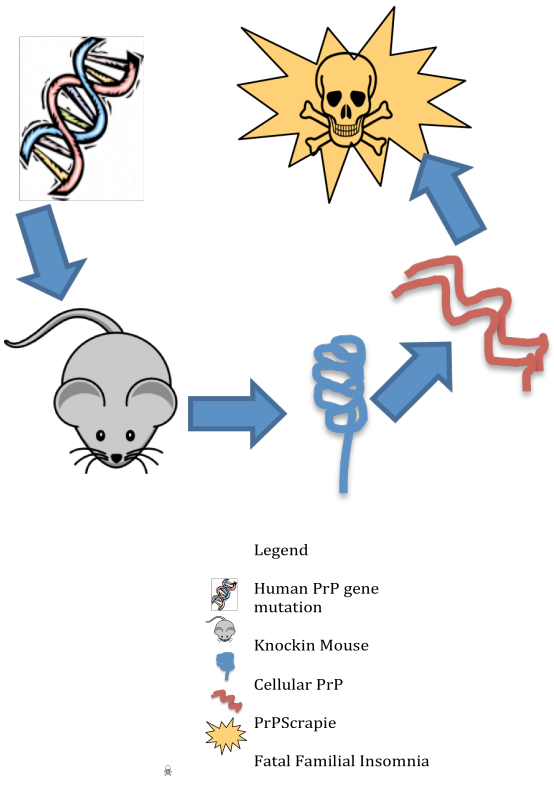

Figure 1. Knockin Insomnia Researchers generated prion disease in a mouse model by knocking in the human PrP mutation associated with Fatal Familial Insomnia (FFI).

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thalamic region of the brain and characteristics such as the spongy appearance caused by the death of large numbers of neurons. The transmission barrier introduced by the researchers also ensured that none of the mice acquired the disease from infection through other pre-existing prions and were actually quite effective in doing so.

The implications of this research are vast and far reaching. Finally, a lid can be placed on the mystery of whether genes can induce spontaneous generation of prions, as this study has conclusively shown. This information is invaluable to the scientific community, as it wields enormous potential in understanding the origins of this relatively new and incredibly diverse disease. It is also applicable not only in elucidating the genetic origin of the disease but also in understanding what genes may code for a higher propensity for the infectious form to cause disease within an organism.

Now that one of the mutations associated with a strain of prion disease has been shown to cause that disease, further studies can potentially map out the genetic origin of other familial strains of prion disease, such as Gerstmann-Straussler-Syndrome. Identification of these genes can then lead to potential therapies that may silence the mutation or produce drugs that reduce the likelihood of the spontaneous generation of infectious prions in these genetically predisposed patients.

Though the occurrence of spontaneous prion disease has a relatively low incidence worldwide, every life counts. Because prion disease's occurrence increases with age and life expectancy has increased drastically in the last century, prion disease will become an increasingly relevant issue. Its prevalence across cultures also demonstrates that the disease is not going to remedy itself anytime soon. A greater understanding of this unique malady will help to combat this recently discovered enemy and stay on top of any curveballs it might throw.

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