NEURODEGENERATIVE DISEASE

Proving the link

Some prion diseases have been associated with familial mutations in the gene encoding the prion protein (PrP). However, how these mutations contribute to the disease process was not well understood. Lindquist and colleagues now show for the first time that mutations in PrP can produce an infectious form of the protein, providing crucial evidence for the 'prion hypothesis'.

Two hypotheses have competed to explain the contribution of PrP mutations to prion diseases: the prion hypothesis predicts that the mutations facilitate PrP misfolding, giving rise to an infectious agent, whereas an alternative theory suggests that the mutations increase susceptibility to infection by exogenous agents. Here, the authors examined the former theory by generating transgenic mice carrying the mouse equivalent of the human PrP mutation that is linked to the prion disease fatal familial insomnia (FFI). Overexpression of PrP can itself cause disease, a potential complication of previous studies of this type. Here, the authors used a knock-in approach (the mutation was introduced into the mouse *Prnp* locus), ensuring that expression of the mutant protein was regulated as wild-type PrP would have been.

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By 18 months of age the mice had developed neuropathology that was distinct from that observed in mouse prion diseases, such as scrapie, and was highly reminiscent of human FFI, particularly the thalamic degeneration component. The proteinase K-resistant form of PrP (PrP^{res}) was almost undetectable in the mutant mouse brains, replicating another characteristic that sets FFI apart from many prion diseases. Furthermore, the mice exhibited distinctive behavioural abnormalities — including sleep disturbances — that differed from those of mouse scrapie and mimicked those of FFI.

To determine whether the FFI mutation resulted in the generation of a transmissible agent, the authors injected brain material from the mutant mice into mice expressing normal or high levels of PrP. Both sets of mice developed neuropathology and behavioural symptoms that were similar to the disease phenotype seen in the mutant mice. Furthermore, the disease could be serially transmitted — brain extracts from the mice injected with the diseased brain material could themselves cause disease in additional mice.

Importantly, the authors took precautions to ensure that the disease pathology that they observed was not a result of increased susceptibility to any infectious agents that might have been in the laboratory environment: in the FFI knock-in mice they 'humanized' the prion sequence by altering two amino acids, creating a transmission barrier to existing mouse prions. Indeed, when mice expressing the humanized PrP were injected with conventional strains of mouse or hamster scrapie prions, they were resistant to the disease.

This study shows that — as predicted by the prion hypothesis — a mutation in PrP can result in the generation of an infectious agent capable of causing a distinct neurodegenerative disease. As well as helping to resolve one of the key issues in prion biology, the development of this new mouse model of FFI might contribute to the understanding of disease mechanisms and potential targets for therapeutic intervention.

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ORIGINAL RESEARCH PAPER Jackson, W. S. *et al.* Spontaneous generation of prion infectivity in fatal familial insomnia knockin mice. *Neuron* **63**, 438–450 (2009)