Prion genetic modifiers in the mouse

https://neurodegenerationresearch.eu/survey/prion-genetic-modifiers-in-the-mouse-2/

Principal Investigators

Dr S E Lloyd

Institution

MRC Prion Unit

Contact information of lead PI
Country

United Kingdom

Title of project or programme

Prion genetic modifiers in the mouse

Source of funding information

MRC

Total sum awarded (Euro)

€ 4,755,722

Start date of award

01/04/2011

Total duration of award in years

5.0

The project/programme is most relevant to:

Prion disease

Keywords
Research Abstract

Prion diseases are characterised by a prolonged incubation period which is determined by many elements including genetic factors. polymorphisms within the prion protein gene (Prnp) are a major genetic influence on incubation time and susceptibility however it is becoming increasingly evident that variation at other genetic loci may also make a significant contribution. The identification of key polymorphisms, genes and pathways will increase our understanding of the underlying principles of prion Biology, provide novel targets for therapeutic intervention and help identify those individuals at greatest risk of developing prion disease.||Linkage analysis

performed to date in various mouse crosses has mapped several genetic loci of interest and our on-going research is aimed at refining these localisations and identifying candidate genes. The use of a heterogeneous stock of mice for genetic mapping has successfully reduced the size of several target regions to 1-2Mb so that a candidate gene approach is now feasible. Genes are evaluated by searching for polymorphisms within the mRNA, intron-exon boundaries and regulatory regions and are tested in the cross to assess their potential contribution to the observed phenotypic variation. Additional analysis may also be done by quantitative gene expression studies between mouse strains in both the unaffected and affected state.||As part of a Unit wide effort, we will test candidate genes for prion disease-related functions using an in-vitro assay whereby the gene function is impaired by RNAi knockdown and the effect on cell susceptibility and prion propagation is determined (Scrapie Cell Assay).||Where a promising candidate gene has been identified, new mouse models are being generated to test in-vivo whether over-expression or knockout of the gene significantly modifies prion disease incubation time as predicted by our genetic analyses.||While mouse models are an invaluable tool, our ultimate aim is to identify the genes and their polymorphisms that also influence susceptibility to various human prion diseases. To this end, quantitative trait genes successfully identified by our mouse studies are being evaluated by haplotype or single polymorphism association studies in our collections of DNA from patients affected by prion disease. In addition, these studies principally aim to understand fundamental processes, and potentially identify new therapeutic targets, which may be of generic importance in neurodegeneration and protein misfolding diseases.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Prion disease

Years:
2016

Database Categories:
N/A

Database Tags:
N/A