ABSTRACT

Principal Investigator: Professor Frances M Platt

Grant Title: Genetic modifiers of sphingolipid biology in health and disease

The aim of the study was to discover genes that modify lysosomal glycosphingolipid biology in health and disease through the systematic analysis of a large number of lysosomal parameters in tissues from different strains of healthy mice. Lysosomes are the centre of cellular degradation and recycling and fundamental for multiple biological processes, including glycoconjugate catabolism. Imbalances in these pathways can generate pathologies e.g. lysosomal storage diseases. However, they have also been associated with common diseases including Alzheimer's and Parkinson's disease. One approach to treat diseases associated with lysosomal dysfunction is to identify modifier genes that protect against the deleterious effects of the primary lysosomal defect. We therefore have been analysing the activity of lysosomal enzymes in a broad range of inbred mouse strains with the aim of mapping modifier loci using a genome wide association strategy. Thus the aim was to identify new genes that increase or modulate the activity of lysosomal enzymes/proteins, i.e. genetic modifiers, to discover new strategies for treating this devastating group of primarily neurodegenerative diseases. In this study we were able to analyse a panel of thirteen lysosomal enzymes from 27 different strains of mice. The data generated is presently being computer-processed in genome-wide association studies (GWAS) to identify candidate genetic modifier genes. This is being done by our collaborator in Chile, Professor Andres Klein. Once identified, these genes will become new targets for the development of new treatments for lysosomal storage disorders.

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