Mapping the genetic architecture of global gene and exon expression in the human brain to understand common diseases

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Title of project or programme

Title of PI	Mapping the genetic architecture of global gene and exon expression in the human brain to understand common diseases

Principal Investigators of project/programme grant

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Source of funding information

Medical Research Council

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36

The project/programme is most relevant to

- Neurodegenerative disease in general

Keywords

Research abstract in English

The aim of this project is to translate newly discovered genetic risk traits for complex neurological and

psychiatric conditions into an understanding of pathogenesis. Until recently there seemed little hope of developing a genetic understanding of common diseases of the central nervous system (CNS). However, whole genome association studies of human disease are revolutionising our understanding of the aetiology of complex diseases, from psychiatric conditions such as drug addiction and schizophrenia on the one hand, to neurological conditions like Parkinson's and Alzheimer's disease on the other. These studies have demonstrated what has long been suspected, that common 'normal' variability contributes to the risk of common neurological and psychiatric disease. While some of the risk loci identified have been assigned to coding changes in genes, the majority have not, and many have not even mapped to recognisable genes.

Thus, knowing genetic risk variants for common diseases has not provided an automatic understanding of pathogenesis or obvious therapies. In order to address this problem we will study the genetic variability of gene expression within the human brain. The basis of our approach is the hypothesis that genetic differences in transcriptional regulation, which are present and measurable in control populations, are important drivers of pathology in the human CNS. If common genetic differences in transcriptional regulation can drive pathology in the human CNS, then we would expect to find strong associations between the risk SNPs identified in GWAs for neurological and psychiatric diseases and specific mRNA expression phenotypes of functional significance in control human brain.

We intend to use post-mortem control human brain tissue to collect samples from well-defined brain regions known to be particularly affected in the most common neurological and psychiatric diseases. Since risk-associated SNPs will be present in the control as well as the case population, using control brain tissue we can study downstream affects on gene expression without the complications of neuronal death, glial response and symptomatic treatments. Using microarray technology, we will produce high quality, genome-wide paired SNP and exon-specific expression data. Data analysis will be focused on identifying downstream gene expression changes associated with individual SNPs known to increase the risk of developing a neurological or psychiatric disease.

Thus, we will bridge the gap between genetic risk and pathophysiology. In this way, we will be able to point towards new therapeutic strategies for the early and effective treatment of human diseases of the CNS.

Lay summary
In which category does this research fall?

- Basic research