Molecular analysis of neuromuscular and neurological disease

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Title of project or programme

Molecular analysis of neuromuscular and neurological disease

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
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- United Kingdom

Source of funding information

Medical Research Council

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6088152.41

Start date of award

01-04-2005

Total duration of award in months

60

The project/programme is most relevant to

- Spinal muscular atrophy (SMA)

Keywords

Research abstract in English

Research is focussed on three areas: (1) the study of dystrophin and dystrophin-related proteins and their role in muscular dystrophy; (2) the molecular analysis of spinal muscular atrophy (SMA); (3) the

use of ENU mutagenesis to study movement and behavioural disorders in man. The absence of dystrophin causes the X-linked recessive severe progressive muscle wasting disease Duchenne muscular dystrophy (DMD). Patients are usually confined to a wheelchair before the age of twelve and die in their late teens or early twenties. The development of therapy for DMD is challenging because dystrophin is a large structural protein that needs to be delivered to all muscles. We are focussing on the pharmacological up-regulation of the dystrophin-related protein, utrophin as well as exon skipping approaches. We are collaborating with Summit plc in the high throughput screening for drugs which might increase levels of utrophin in muscle. One candidate drug, C1100 is being taken forward to clinical trials by BioMarin Pharmaceuticals. We have developed a new mouse model to enable more efficient and faster screens in the future.

The second approach to therapy involves exon skipping using U7snRNA AAV vectors. We have improved the efficiency of exon skipping by adding tails to the exon specific antisense oligonucleotide sequence.

We have completed our studies of the function of the dystrophin binding partner, syncoilin. We have characterised the expression of syncoilin in the spinal cord and nerve. We demonstrate that syncoilin binds peripherin and that it may be involved the formation of peripherin networks. In particular, syncoilin interferes with the function of the isoform of peripherin reported to be associated with ALS. We observed a neuronal phenotype in the knock out mice.

SMA is leading cause of infant death. Many of the genes involved have been identified. We are studying the function of these genes, particularly, SMN in collaboration with Dr Kevin Talbot (Department of Clinical Neurology).

We are analysing several mouse mutants from the ENU mutagenesis programme at the MRC MGU which show movement and behavioural abnormalities. One mutant, name robotic, is a dominant mutant characterised by selective regional Purkinje cell loss in the cerebellum, a jerky ataxic gait, behavioural abnormalities and cataracts. We identified the mutated gene as Af4 which had previously been implicated in leukaemia. Af4 is a member of a family of five genes. All these genes have a role in T-cell development, cellular growth, apoptosis and CNS function. Microarray analysis of laser microdissected purkinje cells indentified the IGF1 pathway as being disrupted. We have demonstrated that the purkinje cell death can be rescued by the administration of IGF-1, implicating the IGF-1 pathway in this form of degeneration. Another mutant has been shown to have a mutation in the Oxr1 gene which is involved in the cellular response to oxidative stress. This is of particular interest since this gene is upregulated in human ALS and mouse models of the disease.

We have identified the bdr mouse with a mutation in SNAP25 as a potential model for schizophrenia. We have demonstrated that these animals have abnormal circadian rhythms which are very similar to those seen in schizophrenia patients. We are currently investigating the gene expression changes which might underlie these observations.

Lay Summary