Mouse Neuromuscular Genetics

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Title of project or programme

Mouse Neuromuscular Genetics

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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01-04-2005

Total duration of award in months

60

The project/programme is most relevant to

- Motor neurone diseases

Keywords

Muscular dystrophy, scoliosis, motorneuron disease,mouse models

Research abstract in English

Our program aims to obtain insights into muscle function, innovation and the mechanism of muscle disease through the identification of genes underlying neuromuscular disorders in the mouse and their functional analysis. The main continuing focus of the programme is to characterise the KY

protein and its role in muscle function. The ky mutation causes muscular dystrophy on postural tonically active muscles and, secondarily, a chronic thoraco-lumbar scoliosis. We exploit traditional molecular biology tools alongside microarray and proteomics techniques to identify proteins that may interact with Ky and investigate the downstream effects of the ky mutation. Interacting partners are then studied in the diseased status to elaborate on the impact of the ky mutation on the expression and localization of those proteins. These studies have already revealed a strong interaction with ?-filamin, a pivotal protein in the mechanism of pathogenesis of several limb-girdle muscular dystrophies. On the other hand, we have also undertaken the mapping and positional candidate cloning of the mouse mutant Trembly, a new syndromic muscle atrophy mutant isolated at Harwell. Genetic and physical mapping of the trembly locus will run alongside RNA and protein profiling and functional positional candidates will be assessed.

Lay Summary

We use mouse mutants to obtain insights into muscle function and the mechanisms of muscle disease. Our studies focus on two mice with distinctive muscle pathologies, ky-kyphoscoliosis and Trembly. The secondary thoraco-lumbar scoliosis developed by the ky mutant is due to the weakness of postural muscles and suggests that this gene should be considered a candidate for causing scoliosis in humans. The genetic defects for most muscle diseases have now been identified. Hence, current efforts centre on the understanding of the biological and pathogenic roles of the variety of proteins associated with muscular dystrophies. Untangling the function of the Ky protein will make a contribution to the studies of molecular pathogenesis of muscular dystrophies. On the other hand, Trembly suffers from widespread muscle atrophy, displays occasional tremors and its neuromuscular junctions are persistently poly-innervated. We aim to identify the genetic defect causing Trembly and proceed with the functional characterization of the underlying protein. Currently, Trembly is undergoing detailed physiological and functionally analysis in order to identify the primary target tissue of this mutation, i.e., either skeletal muscle or peripheral nerve. These studies will clarify whether, in addition to its inherent muscle pathology, Trembly may be a disease model for motor neurone disease.