Investigation of ALS caused by mutant CHCHD10

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USA

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Investigation of ALS caused by mutant CHCHD10

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5

The project/programme is most relevant to:

Motor neurone diseases

Keywords
Research Abstract

Some of the most robust advances in the understanding of amyotrophic lateral sclerosis (ALS), a multi- etiologic and fatal disorder of the nervous system, have come from the identification of the genetic basis of a subgroup of ALS cases. In this subgroup of ALS (familial ALS or FALS), the disease is inherited as a familial trait. Identification of a single mechanism of disease across all of ALS has been elusive, but notable amongst proposed common mechanisms is

mitochondrial dysfunction. However, till recently, no direct robust etiological link between mitochondrial genes, nuclear or mitochondrial, had been found. Recently, others and we found that mutations in a gene called CHCHD10 causes ALS and additional phenotypes. Some other ALS genes, including VCP, HNRNPA1, SQSTM1 and OPTN are also associated with other phenotypes besides ALS. CHCHD10 and its protein product are not well studied. To investigate how a mutation in CHCHD10 may cause ALS, we have collected or developed promising reagents and assembled collaborators and laboratory personnel with specialized skills in genetic engineering, rodent models, cell biology, CRISPR/Cas9 gene editing, mitochondrial function, redox response, induced pluripotent stem cell (iPSC) derived motor neurons and primary motor neurons to carry out the proposed experiments in my laboratory and the laboratories of collaborators. We will investigate the pathology and behavior of a new transgenic mouse model we have engineered to overexpress the mutant (R15L) human CHCHD10 gene. Preliminary study shows axonal pathology in the spinal cord and brain of this mouse with periodic beaded axonal swellings harboring mitochondria. Additional more precise models will also be developed. To determine what aspect of mitochondrial function or morphology is affected by mutant CHCHD10 we will screen mitochondrial function of energetics, redox studies, calcium buffering and electron microscopy analysis. We will identify the binding protein partner(s) of CHCHD10 protein to understand the role of CHCHD10 in the mitochondrial biology. On completion, our study would provide a clearer understanding of the central defect(s) in this form of ALS and potentially a more granular understanding of mitochondrial defect generalizable across ALS. The study will also allow the identification of potential molecular targets for rational therapy and/or prevention of ALS.

Lay Summary
Lou Gehrig disease is fatal. We have found a new cause for it, this flaw directly affects the energy power house (mitochondria) present in neurons. We have also developed pertinent animal models to find the mechanisms of disease so that rational therapies can be rapidly found.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Motor neurone diseases

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N/A

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