Research Project:

NKX6-2 Related Spastic Ataxia and Leukodystrophy: Natural history, biomarkers and the potential of gene transfer methods

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Scientific Summary

Hypomyelinating leukodystrophies are a heterogeneous group of genetic disorders. Recently, this group and others identified bi-allelic mutations in the NKX6.2 gene that cause autosomal recessive spastic ataxia and hypomyelinating leukodystrophy. Since the gene was identified they have extended their analysis of the clinical phenotype to 33 individuals with NKX6-2 mutations from around the world.

NKX6.2 mutations show a varying degree of loss-of-function, which consequently causes dysregulation of CNS myelination. There is currently no disease modifying treatment, clinical or wet biomarkers for NKX6.2 patients, with only supportive care available.

Therefore, in this proposal they plan to extend their genomic analysis to identify further NKX6.2 patients, carry out a longitudinal natural history study to evaluate and understand disease progression and identify serial biomarkers to inform future trials. There is also an important need to develop methods to replace and rescue the loss of NKX6.2 protein, initially through gene transfer methods in patient fibroblasts and then in iPSC differentiated lines.

Lay Summary

Dr Chelban and her team at UCL recently discovered that the genetic cause of SPAX8 is a mutation in the NKX6-2 gene. SPAX8 is a rare ataxia which is characterised by stiffness and problems with coordination. There is currently no treatment or cure for SPAX8, and no way to reliably measure the progression of the condition.

In this project, Dr Chelban and Prof Houlden have planned a number of ways to learn more about SPAX8, and also plan to begin investigating the potential of gene therapy to treat the condition.

They first plan to conduct a natural history study using clinical information from SPAX8 patients. A natural history study involves collecting health information over a period of time (usually years) in order to better understand how a condition progresses. These studies are really important for progressive conditions and are being carried out for a number of different ataxias. They will also use samples from patients, such as blood samples, to find a way of accurately measuring the progression of the condition. This is really important when preparing for clinical trials, because the researcher conducting the trial needs a way of measuring changes in the condition so they can show whether their treatment works.

Importantly, Dr Chelban and her team also plan to study gene therapy for SPAX8. To do this, they will grow cells donated by patients and design ways in which the mutated NKX6-2 gene

can be replaced with a healthy version of the gene. They plan to package the healthy version of the gene into a virus, which is able to infect cells but cannot cause any virus-related health problems. This technique is being studied for a number of conditions and offers real hope for the future of gene therapy. Once the healthy gene has been introduced, they will carry out tests on the cells to see if this could work as a treatment for SPAX8. If successful, they hope that in the future they could test this gene therapy on animal models of SPAX8.

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