Action on FSH Appeal

Introduction

Facioscapulohumeral muscular dystrophy (**FSH) is the third most common muscular dystrophy** affecting over 1,300 people in the UK (and at least 140,000 worldwide). The degree of weakness or disability can vary quite widely between different affected members in a family, but can show even greater variation between people in different families. For some, it can result in weakness not only of facial muscles and shoulders/upper arms, but also of additional combinations from the neck, forearms, wrists, fingers, hips, legs, ankles and the back muscles.

There is currently **no treatment or cure for FSH**.

Over the last five years, the Muscular Dystrophy Campaign has invested over £100,000 to help fund work that has pinpointed the location of the mutation causing FSH. It is essential to fully understand the underlying cause of FSH and how it can progress to develop future treatments and cures. The Muscular Dystrophy Campaign's Action on FSH Appeal is supporting two critical research projects that will further our understanding of FSH and we are seeking donations to enable us to complete this vital work in the year ahead. As well as this, we are also looking to raise £25,000 to fund a new FSH registry in the UK.

Background: The Muscular Dystrophy Campaign

The Muscular Dystrophy Campaign was founded in 1959 as a medical research charity seeking to discover the causes of, and find a cure for, muscular dystrophy and related neuromuscular conditions. The charity is now the leading voice on neuromuscular research in the UK, with an exciting research programme that covers all forms of muscular dystrophy and related conditions. We invest more than £1million each year, with more than 20 live projects taking place at any one time – from basic science to clinical pilot studies. Since our foundation, our funding of basic science has led to the identification of many genes that cause muscle-wasting conditions, which in turn has led to improved diagnosis and care and has given scientists a better understanding of muscle function. The goal of finding viable treatments and cures remains at the very heart of the research the Muscular Dystrophy Campaign funds.

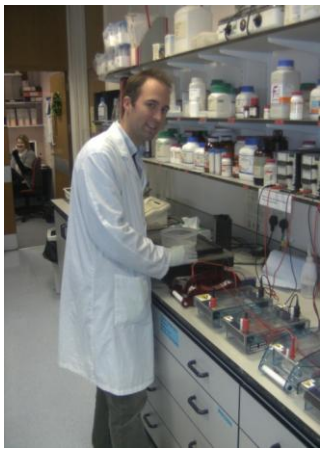
Funding high quality research

To ensure that we fund only the highest-calibre clinicians and most promising research, PhD studentship and Clinical Research Fellowship applications are subject to our standard assessment process. The detailed scientific applications are sent for peer review by experts in the field and the shorter, lay application assessed by our Lay Research Panel.

Project 1 - Understanding the molecular causes of FSH

Professor Jane Hewitt, University of Nottingham

Professor Hewitt is using this 4 year PhD studentship to further the understanding of the molecular mechanism behind FSH. There is currently no treatment for FSH and there has been little progress in this area, mainly due to the complex and unique nature of the mutation. The increased understanding of the underlying mechanism behind FSH will help towards future development of potential therapeutic approaches for this condition.



Next-generation DNA sequencing

As part of Professor Hewitt's work Andreas Leidenroth, a member of her lab is using 'next-generation DNA sequencing' technology to correct diagnoses. This enables patients to gain, for the first time, a precise genetic diagnosis. In the past scientists were required to individually test a small number of genes that are known to be involved in other muscular dystrophies one by one, which can be time consuming and limits the search to a small number of genes, at the risk of missing the mutation. Andreas uses a revolutionizing machine: A 'next-generation DNA sequencer' which is a powerful diagnostic tool. Rather than just reading the code of a single gene at a time, these machines can simultaneously decipher all 25,000+ genes. However human DNA is quite variable from one person to the next, therefore the team are then also required to use different data filters to carefully narrow down the possibilities.
Aim: To give us a greater understanding of exactly why the mutation is causing the symptoms of FSH

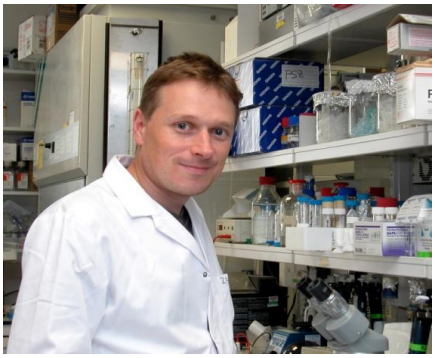
A precise genetic diagnosis is important because it enables clinicians to give a more accurate prediction of how the condition will progress and it allows families to plan for the future, potentially allowing them to take advantage of prenatal and pre-implantation genetic diagnosis when planning to have children. Importantly, if treatments such as gene therapy become available in the future, a precise diagnosis will be required so that patients can access the appropriate treatment.

For many years, researchers thought that the repeated sequence did not contain a gene but more recent research has suggested that this may not be the case. Part of the D4Z4 repeated region contains the instructions to make a protein. This suggests that this region does contain a gene after all. Prof Hewitt is studying the D4Z4 region further in order to understand more about the protein that is produced. She will look at the production of the protein in both healthy and FSH cells, in the hope of discovering more about its function. She will also investigate if the deletions seen in FSH change the amount of the D4Z4 protein being produced.

How will the outcomes of this research benefit patients?
We hope that this project will increase our understanding of the very complicated mechanism behind FSH. This is being elucidated one small step at a time, and the more we understand about it, the more likely researchers are to be able to develop a treatment.

Project 2 - Investigating the role of muscle stem cells in FSH

Dr Peter Zammit, King's College London



Dr Zammit is using this 4 year PhD studentship to explore the role that muscle stem cells have in the progression of FSH. Dr Zammit will deliver two of the genes thought to be involved in FSH into stem cells. This will allow him to find out what effect, if any, these genes have on how well the stem cells are able to repair muscle.

What will they do?

The role of muscle stem cells is to maintain and repair skeletal muscle. Researchers have been investigating the possibility of manipulating muscle stem cells to use them as a treatment for various forms of muscular dystrophy. Many aspects of muscle stem cell behaviour, however, are still not well understood and some major challenges remain. Muscle maintenance and repair by muscle stem cells does not work properly in FSH and it is thought that this may directly contribute to the disease progression.

The exact function of the repeated section of DNA in FSH individuals is unknown and a number of ideas exist as to what they may do. One idea is that by deleting some of these repeats, an abnormal protein is made (called DUX4). Another idea is that the loss of repeats affects neighbouring genes (e.g. DUX4c) and this affects how the muscle cell functions. Dr Zammit aims to find out if DUX4 and DUX4c affect how well the muscle stem cells are able to repair and regenerate muscle. Abnormal functioning of these genes could interfere with normal muscle stem cell function by either activating other genes at the wrong levels, time or place, or interfering with the operation of other important genes.

Dr Zammit and his student will deliver DUX4 and DUX4c into muscle stem cells and manipulate their activity in order to determine if they alter the ability of these cells to function normally. They will also examine how they affect other genes and in particular those that are important for maintaining normal muscle stem cell behaviour.

How will the outcomes of the research benefit patients?

This research is important as it gives scientists more information on how the genetic fault that causes FSH affects muscle and the way the muscle is able to repair and regenerate. It will also give important information on the viability of using muscle stem cells as a treatment for FSH in the future.

FSH Registry

Patient Registries

What are patient registries?

Patient registries are databases that contain information about individuals affected by a particular condition. Most registries focus on the information that is needed to find patients eligible for clinical trials, but they have many other benefits. The information they contain can help clinicians develop care standards and patients can link to the research community and have the opportunity to access information directly relevant for their condition.

The Muscular Dystrophy Campaign is working with TREAT-NMD to set up a new registry for people with FSHD. A curator based in Newcastle has been in post since the beginning of 2012 to manage this registry, but the Muscular Dystrophy Campaign is now looking for funding to take this project forward.

FSH Registry

The Muscular Dystrophy Campaign will be calling on everybody in the UK with FSHD to join this new patient registry. The new registry will allow clinicians and researchers to speed up the transition of treatments from the laboratory to the clinic by speeding up the recruitment process of people to take part in clinical trials and ultimately to improve understanding of the condition.

Researchers have made considerable progress in recent years with the development of promising technologies that could provide the basis for potential treatments for FSHD. To find out whether any of these new technologies can be used to treat the symptoms of the condition, they have to be tested in a clinical trial. FSHD, however, is a rare disease and one of the problems clinicians will face is in finding enough patients for clinical trials to start without delay.

The registry, which will be established under the lead of Professor Hanns Lochmüller at Newcastle University, is a centralised database that contains the crucial information needed to find people suitable for clinical trials. The information will also be used to develop standards of care and will give people a link to the research community, as well as the opportunity to access information directly relevant to their condition.

Action on FSH Appeal

We are currently seeking donations to ensure that the Muscular Dystrophy Campaign can complete these two important research projects in their final year. These first two projects last four years and our fundraising target is £20,000 to fully fund the remaining year of each project. On top of this, we are also looking for £25,000 to fund the new FSH registry.

	Project 1	Project 2	Already received	Total left to raise
Year 1	25,000	15,000	40,000	0
Year 2	25,000	15,000	40,000	0
Year 3	25,000	15,000	40,000	0
Year 4	5,000	15,000	0	20,000
Total project cost	**80,000**	**60,000**	**120,000**	
FSH Registry				**25,000**
Appeal total				**45,000**

Help us to raise £45,000 by:

- Making a one-off donation
- Committing to a regular monthly donation
- Introducing us to a grant making trust
- Introducing us to a business donor or recommending us as your Charity of the Year

Making the most of your gift

The Muscular Dystrophy Campaign can claim Gift Aid from the Inland Revenue on all eligible donations made by individuals.

All donations are very much appreciated, thank you. We would be delighted to recognise your support in communications related to the FSH appeal if wished. We will provide regular progress updates and a research laboratory visit to all those who contribute to this appeal.

Donations can be made online at the FSH-MD Support group UK website at http://fsh-group.org/ or via the groups "My Donate" Page at: https://mydonate.bt.com/fundraisers/mdcfshsupportgroupuk

For further information about the appeal please contact.

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