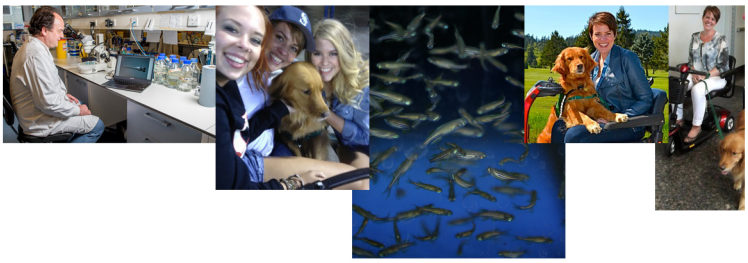
Issue 4
July 2014

GLOBAL FKRP REGISTRY

Newsletter



REMEMBER TO UPDATE YOUR INFORMATION

The Registry is only as good as the information held within it so it is vital that you keep your records as up to date as possible.

Since patients with FKRP mutations are rare, every single person counts!

Welcome to the fourth Global FKRP Registry Newsletter!

What's inside?

New Registry Logo

We have tried to give the Registry an identity of its own and the first step was to have a logo that captures the important aspects of the Registry. The Registry is an important tool in linking the FKRP community around the world, making sure that the people with these very rare conditions are represented by capturing this information in one central place. We hope that you like it!

GLOBAL FKRP REGISTRY

We are also making some changes to the Registry website and health questionnaires and we will let you know about these in due course. Keep a look out in your inbox for another newsletter!

Patients' Stories

The Registry will be starting a library of patient stories, with a summary featured in the newsletters and the full story published on the Registry website.

The first story is from someone with LGMD2I and they have kindly shared their journey from the long path to diagnosis to what their life entails now.

My life with LGMD2I – Anonymous
(full story on the website)

1. Youth
As a baby I was very weak but I grew up fairly normally, albeit always under the normal weight until my twenties. When I was eleven I realised big deficiencies in sports and I was very slow at running and was under average in athletic sports, which led me to be badly teased by my classmates. I started to hate sports because it was always embarrassing for me. After sport lessons I found I always had intense muscle pain. When I was eighteen I discovered other sporting activities like cycling, mountain hiking, skiing and dancing. Neither my parents nor my doctors ever had the idea that there was something wrong with my muscles.
...
6. Philosophy
Thanks to the support of my wife, family, and friends, and last but not least my doctors, I was able to master and enjoy life although having a severe disability. I was lucky since the impact of LGMD2I hit me relatively late and mildly. I know people with LGMD2I who are permanently in a wheelchair by the age of 30 years old, while I was able to ski up until my mid-forties. However, I think it is also a question of mind how to master the terrible fate of muscular dystrophy. This is my philosophy:

- "You've got to know what the heck is going on"
- A "this does not work" attitude doesn't work
- Necessity makes us inventive!
- Never give up
- Be optimistic
- Be independent as much as possible and ask for help when necessary
- Use disability aids as needed
- Fight!
- Enjoy life!

If you would like to share your story then don't hesitate to get in touch with us.

Research Updates

Gene therapy studies in mouse models of LGMD2I

Dr. Qi Lu, at McColl-Lockwood Laboratory for Muscular Dystrophy Research, Carolinas Medical Center, has published two papers showing pre-clinical evidence that gene replacement therapy for FKRP-related muscular dystrophies could have therapeutic potential. Using a mouse model of LGMD2I that he created in his laboratory, his team first demonstrated, in a paper published last October, that it is possible to improve muscle function after introducing a normal copy of FKRP through the use of a benign viral vector (Adeno-Associated Virus or AAV). Then, more recently, using this same mouse model, they compared the effects of the introduction of FKRP or LARGE gene. They showed that LARGE overexpression, like FKRP, can also correct the glycosylation defect in the FKRP mouse model. Long-term studies are now needed in order to assess the efficacy of LARGE up-regulation in improving muscle function and to determine whether there are any deleterious long term effects of LARGE gene therapy. These studies offer a very encouraging animal proof of concept that gene therapy approaches could one day be used to treat FKRP-related muscular dystrophies, such as LGMD2I. Several laboratories are currently pursuing these approaches with the goal of bringing them to clinical trials within the next few years.

Magnetic Resonance Imaging: an objective tool to measure disease progression in LGMD2I

A study has been carried out using a technique known as Magnetic Resonance Imaging or MRI, (see explanation below) to determine what changes occur in the muscles of patients with LGMD2I, and to also to determine whether MRI can be useful to monitor disease progression compared to standard physical assessment techniques.

Magnetic Resonance Imaging (MRI) = type of scan that uses strong magnetic fields and radio waves to produce detailed images of the inside of the body. The technique is widely used in hospitals for medical diagnosis, staging of disease and for follow-up without exposure to ionizing radiation, such as X-rays and CT scans.

The study was carried out at four European referral centres: Newcastle, UK; London, UK; Copenhagen, Denmark; Paris, France.

The first part of the study compared two MRI techniques to see if one is better at characterising the muscles of LGMD2I patients and possibly explaining any gender differences. Thirty eight patients (19 male:19 female) who were all still walking were included in the study, all with the homozygous mutation (c.826C>A) in the FKRP gene. The thigh and lower leg muscles of all patients were assessed using MRI.

Homozygous mutation (c.826C>A) = an identical change (mutation) on both alleles (copies) of the gene, one maternal (from the mother) and one paternal (from the father). c.826C>A is the notation for the specific mutation that has occurred - this is the most common mutation that occurs. Inclusion into studies such as this one is the reason why the Registry collects information on specific mutations.

This study confirmed that the muscles at the back of the thigh (hamstring muscles) are most affected, which has been shown in previous studies, but also highlighted that there are differences between men and women, in not only in the specific muscles that are affected, but also to what extent. This means that female patients could present and progress differently to males.

The second part of the study was looking to find out if a specific type of MRI could be used to determine the progression of disease compared to conventional assessments, such as muscle strength measurements, the 6 minute walk distance (6MWD), and lung function tests (Forced Vital Capacity – FVC). An MRI was carried out 12 months after the initial MRI, as described above. The change in the ratio of fat to muscle in the legs over the 12 months was determined in all patients. This was then compared with the changes observed using conventional assessments.

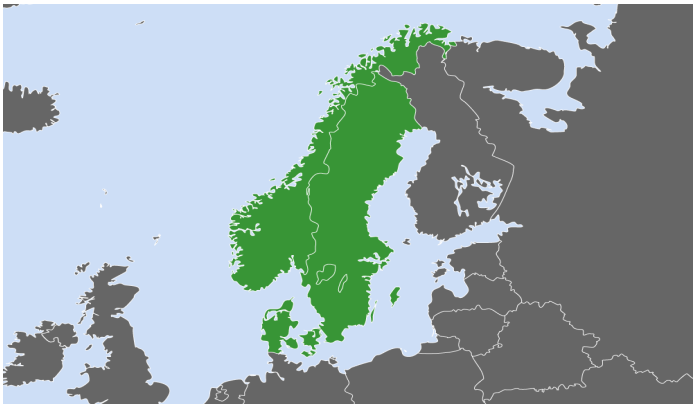
Over the 12 month period, a significant increase in the amount of fat, in 9 out of 14 of the leg muscles analysed, was shown using MRI. Such clear changes over the same time period were not seen in any of the conventional assessments.

This study has demonstrated that MRI is more sensitive in determining changes in the course of the disease, otherwise not shown with the standard assessment methods currently used, over a short time period. MRI is non-invasive, objective and does not rely on patient effort compared to the clinical and physical assessments that are currently used. Muscle MRI could be used to assess which muscles are affected and to what extent, and to monitor how effective new therapeutics are in patients with LGMD2I.

Academic article 1

Academic article 2

Scandinavia – why are these countries so important to the Registry?



Some diseases can be more common in certain countries than others due to the nature of the mutations that cause the disease. For FKRP-related muscular dystrophies the countries that have the greatest number of patients are in Scandinavia - Denmark, Norway, and Sweden. The reason for this is because of something called a "founder mutation" – a mutation that appears in DNA of one or more individuals who are founders of a distinct population. The founder mutation in the FKRP gene has probably been spread by the Vikings, explaining why it is so common in Scandinavian countries. As explained

above the most common mutation for FKRP-related muscular dystrophies is a homozygous mutation written as: c.826C>A.

The patients in these countries have been studied in more detail than most others in different parts of the world and so the total number of people affected by FKRP-mutations is still unknown throughout the world. The main aims of the Global FKRP Registry is to understand how many people are affected by these conditions throughout the world, try to understand where there are differences in care and quality of life, and to attempt to determine if there are any relationships between disease progression and the underlying genetic mutation, especially if this differs from the common mutation.

Future clinical trials will be likely to take place in these countries due to the large numbers of patients and so it is vitally important that we ensure that this population is "clinical trial ready", meaning that patients' current status are well characterised and their genetic information collated.

We are in touch with colleagues from Denmark, Norway and Sweden and are working on ways to raise awareness about the Registry in these countries, or work with national neuromuscular registries already in place.

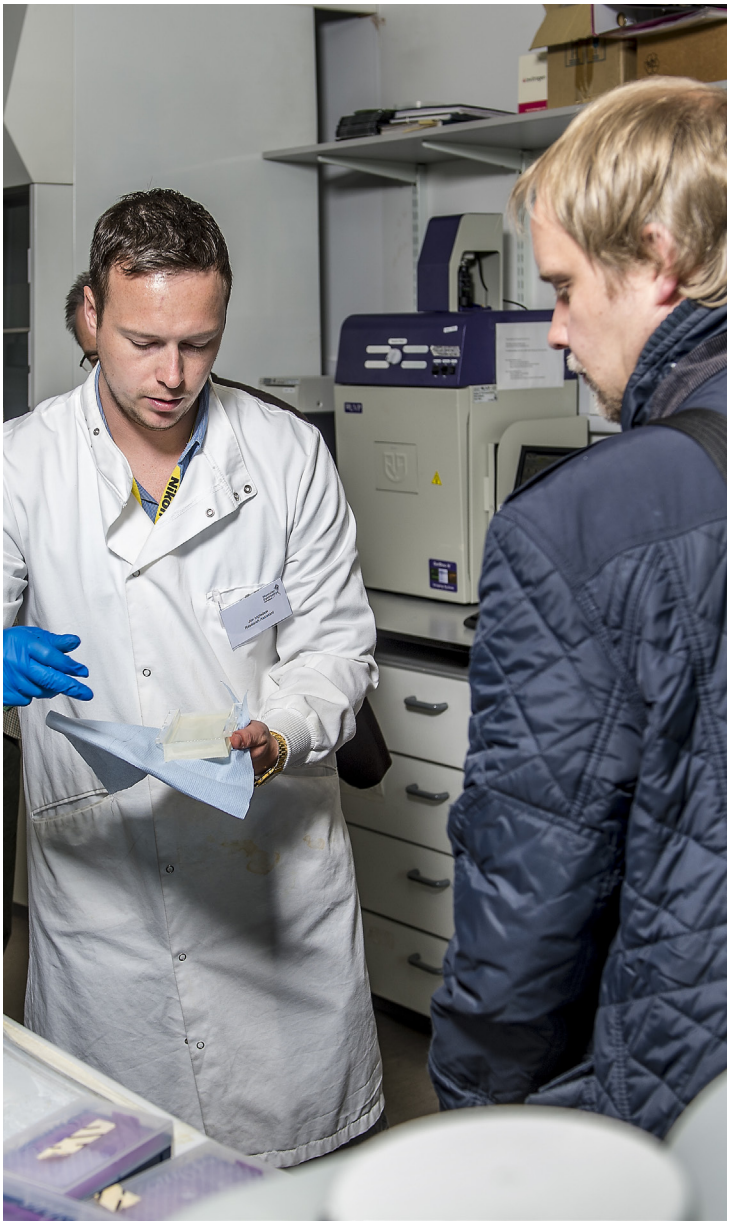
RD Connect update

RD-Connect is a European project focused on linking up databases, registries, biobanks and clinical bioinformatics data (the science of collecting and analysing complex biological data) used in rare disease research into a central resource for researchers worldwide.

Their major goal is to produce a central hub that can accelerate studies looking at the discovery of new genes, enhance the accuracy of diagnoses and aid the development of treatments by making data generated available to the wider community.

Contributing data to a larger platform in this way will ensure that data on patients in these registries is not fragmented and that clinical information, genetic information, data from research studies and biomaterial samples are connected and available. Linking up this data allows researchers to gain a better understanding of the diseases without having to collect all of the information from scratch and from multiple sources.

As part of the RD-Connect project a group has been set-up to outline what the current status for rare disease registries is and develop standard strategies to incorporate data from all of these registries into the central hub. The Global FKRP Registry has been asked to join this group, called the Core Implementation Group for Registries (CIG), as a "Gold Standard" registry. The Global FKRP Registry Steering Committee reviewed the request and agreed to the Global FKRP Registry becoming part of the CIG. The Registry will work with RD-Connect to develop the necessary procedures and protocols to ensure that already existing registries are able to join the platform and can contribute data.



LGMD2I Patient Network update

As mentioned in the last Newsletter (Issue 3), we are in the process of creating an online portal, the "LGMD2I Patient Network", where patients can track their health and environment information in real-time. An initial pilot study with 8 LGMD2I patients will run for one month, during which patients will input their data on a series of predetermined parameters (like number of falls, hours of sleep, medication taken, etc), besides entering any other information they want to track. They are also wearing a device/pedometer to capture their number of steps per day. At the end of this pilot trial, we will collect feedback about the portal and assess what works or not, how we can improve tracking, levels of compliance, etc. We will then use the feedback to build the portal that will be launched to the entire LGMD2I community. Stay tuned!

Meetings and events

Upcoming meetings

- Dystroglycanopathies Family Conference – 19 July 2014, Iowa, USA
- Muscular Dystrophy Campaign's National Conference – 18 October 2014, Coventry, UK
- Clinical conference, 31 October-1 November 2014, Norway

  Abstract to be submitted. Attendance at this conference will allow the Registry to specifically speak with the relevant health professionals involved in the care of patients living in Norway, one of the key countries for the Registry.

Feedback on previous meetings

- Rare Disease Day 2014 - check out the video!
- MDA Clinical Conference, 16-19 March 2014, Chicago, USA

  A poster about the Global FKRP Registry was presented at this year's conference. The conference, normally held every two years, was mainly attended by doctors, physiotherapists, genetic counsellors, and registry representatives. Conferences like this are a good way to speak with the health professionals involved in the care of patients with FKRP-related MDs and make them aware of the Registry. Videos, photos and blogs are available from the conference.

Don't forget that you can get in touch with us if you have any questions. Choose the appropriate national contact from the list below:

Australia - australia@fkrp-registry.org
Belgium - belgium@fkrp-registry.org
Brasil - brasil@fkrp-registry.org
Canada - canada@fkrp-registry.org
Catalan - catalan@fkrp-registry.org
Croatia - croatia@fkrp-registry.org
Czech Republic - czechrepublic@fkrp-registry.org
Denmark - denmark@fkrp-registry.org
France - france@fkrp-registry.org
Germany - germany@fkrp-registry.org
Hungary - hungary@fkrp-registry.org
Italy - italy@fkrp-registry.org
Japan - japan@fkrp-registry.org
Netherlands - netherlands@fkrp-registry.org
Norway - norway@fkrp-registry.org
New Zealand - nz@fkrp-registry.org
Spain - spain@fkrp-registry.org
Switzerland - switzerland@fkrp-registry.org
Taiwan – taiwan@fkrp-registry.org
Ukraine – ukraine@fkrp-registry.org
United Kingdom – uk@fkrp-registry.org
USA - usa@fkrp-registry.org

You can also contact the Registry Coordinator on the following email address:

coordinator@fkrp-registry.org

Let us know if there is anything that you would like to see included in the next newsletter.

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