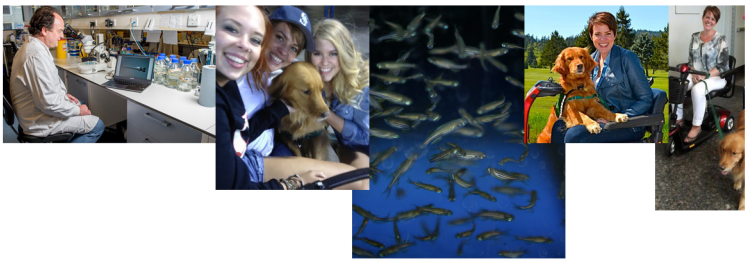
Issue 5
Nov 2014

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 fifth Global FKRP Registry Newsletter!

What's inside?

Global FKRP Registry statistics

There are 324 patients registered, of which 177 are female and 147 are male, from 30 countries (**Figure 1**). Germany (30%), USA (26%), and the UK (14%) represent the largest number of patients. As mentioned in the previous newsletter the Scandinavian countries are still very under-represented in the registry as you can see from the low number of patients from Denmark, Norway and Sweden. The age range with the most patients is 40-49 years with the range of ages spanning from 0-9 to 70-79 years (**Figure 2**).

Looking at the year on year recruitment numbers (332) (**Figure 3**) this differs from the number of patients currently registered (324), mainly because some people have registered but have not in fact had an FKRP-related MD and so with their permission their account has been removed.

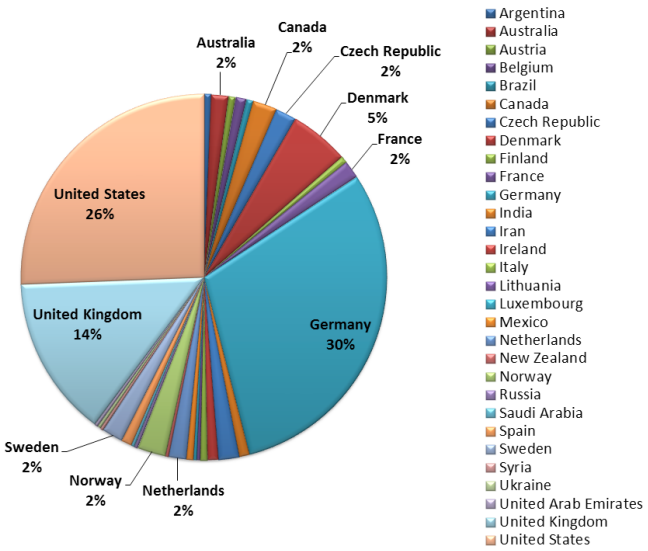


Figure 1. Pie chart showing the percentage of registered patients from each country.

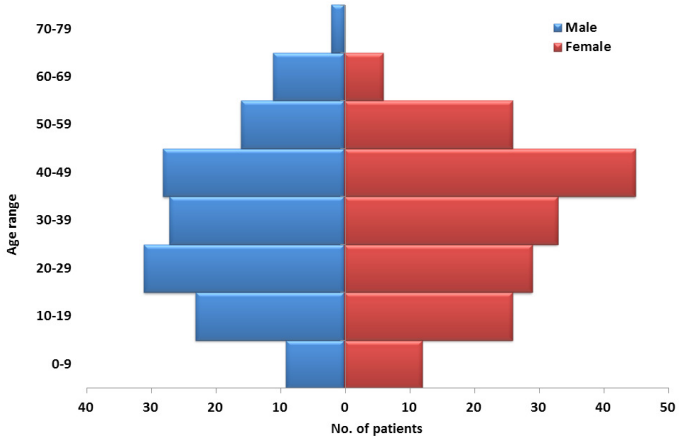


Figure 2. Age range of registered patients for males and females

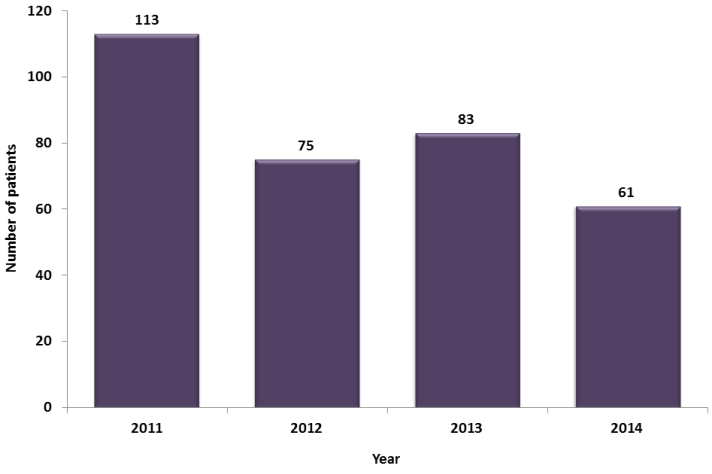


Figure 3. Number of patients that have registered per year

The most common diagnosis is LGMD2I (90%) with the remaining patients reported as having MDC1C (4%), another FKRP-related MD (3%) or the diagnosis is unknown (**Figure 4**). Not all of these diagnoses have been genetically confirmed and so at present we can only say for certain that 148 patients (less than the total of 324) in the registry definitely have an FKRP-related MD. This shows how important it is for us to have a copy of your genetic report as without it we won't know if you are eligible to be included in a clinical trial or research study.

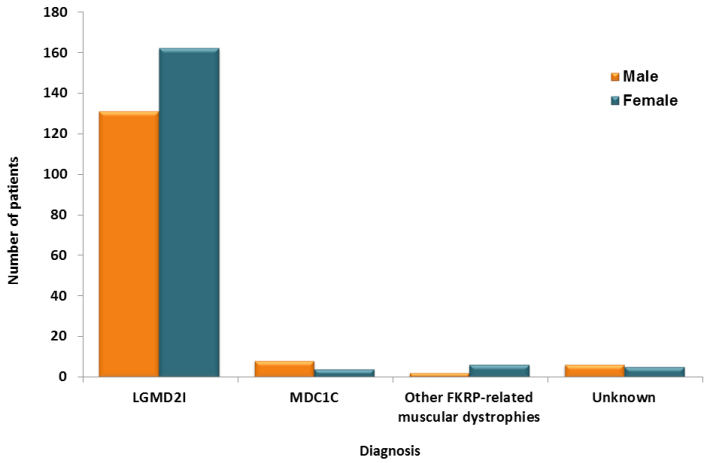


Figure 4. Bar chart showing the representation of each diagnosis as reported by patients.

Genetically confirmed patients

The Global FKRP Registry has been set-up to make it easier to find patients for clinical trials and research studies and so it is essential that we not only know what conditions patients are affected by but also the specific mutation that is causing the condition. This is done by genetic report (also known as molecular report or DNA laboratory report) or by confirmation in a clinical letter from your doctor. All you need to do is send a copy to us and we can enter the information into the Registry for you.

The total number of patients that have therefore been confirmed as having an FKRP-related MD is 148, of which 79 are female and 69 are male, and these represent 19 different countries. 98% of these patients have LGMD2I, 1% MDC1C and 1% have reported their diagnosis as unknown (**Figure 5**).

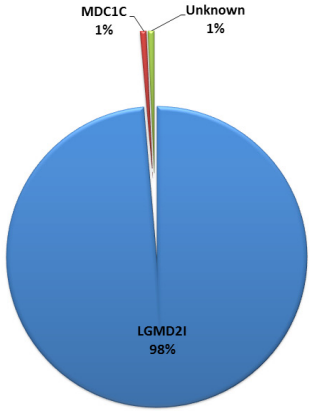


Figure 5. Pie chart showing the representation of each diagnosis as reported by patients, for all genetically confirmed patients.

The age range with the most patients is 40-49 years and this time the oldest patients are in the 60-69 years age range (**Figure 6**).

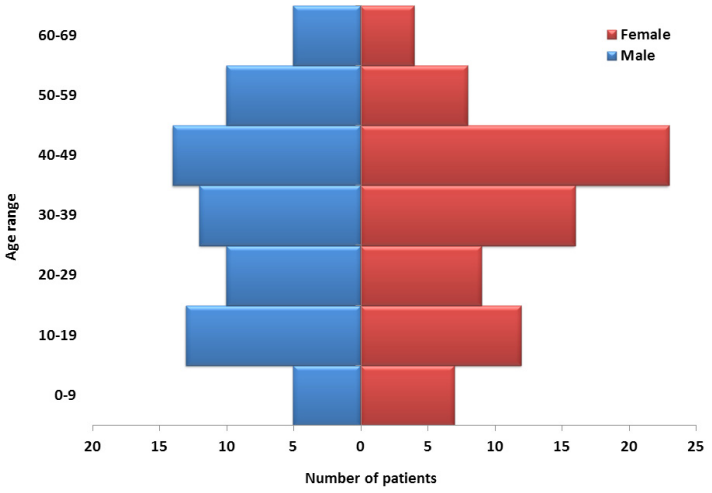


Figure 6. Age range of registered patients for males and females, for all genetically confirmed patients

Family history is very important when looking at genetic conditions and so we looked at the number of patients (genetically confirmed as having an FKRP-related MD) who have an affected family member. 37 said that they did have a family member also affected by an FKRP-related MD, and 110 said that they didn't know of any family members who were affected (**Figure 7**).

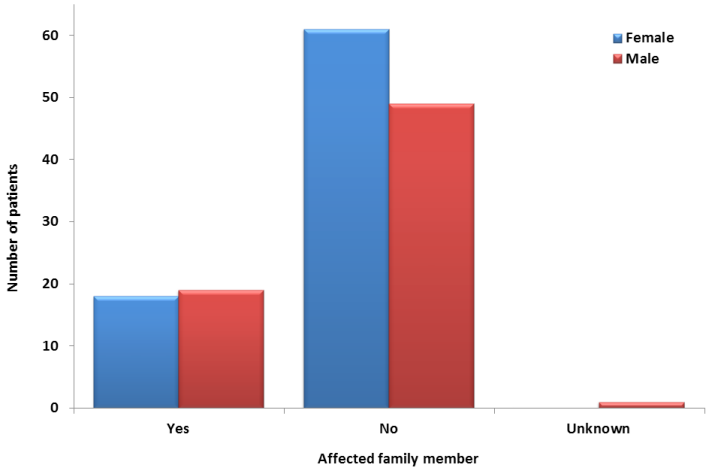


Figure 7. Number of patients with affected family members by male and female, for all genetically confirmed patients.

Patients' stories

We have two new stories to share with you. As mentioned in the previous newsletter we have started a library of patients' stories which we will be publishing on the Registry website and sharing with you in the newsletters.

If you have anything that you would like to share then please get in touch.

"It was my party trick" by Melissa Grove

"As I breezed out of my physical with flying colors, I thought I would show the cute doctor my party trick that had been all the rage at the college parties I was attending. "See? My hip pops out of its socket. Isn't that wild?" "Why don't you come back in and let me see that again?" he asked, tilting his head to the left and then to the right.

Imagine my surprise when he told me he wanted to run more tests, that that was not normal and it definitely wasn't just being double jointed like I proposed. One test led to another: from probes and blood work, to shocks and finally a muscle biopsy....." ***Read more***

"It's part of me" by Lacey Woods

"When I was first diagnosed with muscular dystrophy, I lived in complete denial. I didn't want anyone to know and I made excuses why

I had difficulty walking up stairs or said I was just clumsy from my frequent falls. I wanted to be "normal," a normal wife and mom. I was pretending to be someone I wasn't, and didn't fully embrace the true me. As the disease progressed, I couldn't hide the fact that I was different, I felt like a failure, that it was my fault. It took some time for me to understand that it was a genetic mutation that I had no control over. I became aware of how much energy I was wasting by denying my reality rather than accepting it....." ***Read more***

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

Research updates

Anti-dystroglycan antibody

In collaboration with Dr. Susan Brown at the Royal Veterinary College, Dr. Glenn Morris' group from RJAH Orthopedic Hospital in the UK has recently developed and characterized a new monoclonal antibody against α-dystroglycan (aDG). This new antibody, called DAG-6F4, was tested and compared to other antibodies against glycosylated aDG. DAG-6F4 staining seemed less affected in limb-girdle MD patients than in congenital MD patients. Unlike the commonly used IIH6 antibody against aDG, DAG-6F4 antibody staining was unaffected in a patient with LARGE mutation. These results suggest that the DAG-6F4 antibody may have applications in the diagnosis of dystroglycanopathies. This new antibody is available to the research community through the "Monoclonal Antibody Database" at the Wolfson Centre for Inherited Neuromuscular Disease (http://www.glennmorris.org.uk/mabs/WCIND.htm).

Highlights from the World Muscle Society Conference

The World Muscle Society (WMS) Conference is held every year and is the largest meeting for neuromuscular-related research, with researchers from all over the world attending. The WMS is a multidisciplinary scientific society dedicated to advancement and dissemination of knowledge in the neuromuscular field for the benefit of patients. This year's meeting was held in October in Berlin, Germany. A list of some of the posters and presentations relevant to the FKRP-related MDs is below with a short summary for each.

- ***Limb girdle muscular dystrophy in Sweden***
  Balcin H, Lindberg C, Lindvall B, Sundström A, Solders G.
  The Swedish National Inpatient Register was used to investigate the epidemiology (the study of patterns, causes and effects of health conditions) of LGMDs and it was found that the most prevalent subtype was LGMD2I.

- ***The Italian Registry of LGMD: Natural history genotype-phenotype correlations and outcome measures***
  Magri F, Govoni A, Brusa R, Angelini C, D'Angelo MG, Mongini T, et al.
  Detailed clinical information was collected on 467 Italian LGMD patients from 8 neuromuscular centres in Italy. LGMD2I was found to occur with a frequency of 9.6% and those patients were found to have a 50% chance of having a problem with their heart. Disease onset was found to start on average at 37 years old. This study showed the frequency of LGMD2I in the Italian population and provided improved knowledge about the clinical picture to allow for better care of these patients.

- ***Slowly progressive motor and respiratory dysfunction resulting from FKRP-mutations: a natural history study***
  Crockett CD, Stephan CM, Mockler SRH, Laubscher KM, Zimmerman BM, Mathews KM.
  A natural history study was used to follow a group of 43 patients, with conditions caused by mutations in the *FKRP* gene, for up to 9 years. Standardised assessments were used. Disease progression was highly varied but disease onset was significantly later for those who were homozygous for the common mutation c.826C>A (median age of onset = 11 year, 21 patients). The range in the variability of disease progression was not fully explained by the causative genetic mutation alone, meaning that the slow and variable progression of these conditions creates challenges for designing clinical trials.

- ***LGMD2I: Is there a relationship between clinical phenotype, morphological alterations and level of alpha-dystroglycan glycosylation in patients with the same FKRP genotype***
  Lindal S, Stensland E, Rasmussen M, Jonsrud C, Brox V, Maisoon A, Nilssen Ø.
  Muscle biopsies were obtained from 25 patients with LGMD2I, all with the common mutation c.826C>A. An analysis on the muscle biopsies was carried out and there was no correlation found between the age of disease onset or duration of disease at the time of the biopsy versus the structural changes found in the muscle. The variability in the clinical progression and the changes seen in the muscle biopsy seen in LGMD2I patients with identical mutations in the *FKRP* gene must therefore be explained by other genetic or environmental factors.

- ***Efficient AAV-mediated transfer of FKRP in a new mouse model of LGMD2I***
  Gicquel E, Richard I.
  A mouse model for LGMD2I was developed that mimics the low levels of alpha-dystroglycan glycosylation caused by mutations in the *FKRP* gene, as seen in LGMD2I. The mouse model carried the frequent mutation (c.826C>A) seen in LGMD2I and showed reduced levels of alpha-dystroglycan glycosylation, showing that it is in fact a good disease model. To evaluate gene therapy as a therapeutic approach, the *FKRP* gene was cloned into an AAV vector and injected into the mouse model. Expression of the gene was observed as was restoration of alpha-dystroglycan glycosylation and muscle function was also shown to be improved.

pro2i steroid trial update

In previous newsletters we told you about a proposed steroid trial in LGMD2I patients that we were hoping to obtain funding for. Unfortunately after exhausting all possible options we are unable to secure any funding for the trial at this time. We will keep trying and of course we will keep you informed of any progress we make.

Neuromics

NeurOmics

Neuromics aims to revolutionise diagnostics and develop new treatments for ten major neuromuscular (NMD) and neurodegenerative (NDD) diseases. The diseases included in the neuromics project are listed below.

- Ataxia
- Congenital muscular dystrophy
- Congenital myasthenic syndrome
- Fronto-temporal lobe dementia
- Hereditary motor neuropathies – Charcot-Marie-Tooth disease
- Hereditary spastic paraplegias
- Huntington's disease
- Muscular channelopathy
- Muscular dystrophy – DMD, FSHD and LGMD
- Spinal muscular atrophy – Lower motor neuron disease

It will bring together leading research groups in Europe and will use the most sophisticated –omics technologies. The aims of the Neuromics project are to increase the number of patients with a genetic diagnosis; develop biomarkers for clinical application; improve understanding of functional changes associated with a disease (pathophysiology) and identify drug targets; identify disease modifiers; develop targeted therapies; and translate findings to other, related disease groups.

"-Omics" technologies = techniques used to measure some characteristic of a large family of cellular molecules, such as genes or proteins. They have been named by adding the suffix "-omics". For example genomics – the study of genes and their function, proteomics – the study of proteins.

Sequencing of LGMD patients

Ensuring correct genetic diagnosis for patients with muscle diseases is important to allow for correct disease management, particularly important in the limb girdle muscular dystrophies (LGMD) as they share common symptoms but are caused by a large number of different genes.

There are now two projects that are focused on sequencing DNA to allow for a diagnosis for patients with limb girdle weakness. One project is based in the USA – LGMD-diagnosis.org, and one is based in Europe – MYO-SEQ.

LGMD-diagnosis.org

Several family foundations have come together to help people living in the USA suffering from various forms of LGMD to obtain a specific diagnosis by offering free genetic testing. The large genetic diversity, high costs of genetic analysis and refusal of some health insurance companies to cover genetic diagnosis of these diseases prevent many individuals from obtaining a definitive diagnosis. The programme begins with a preliminary study of 100 eligible US residents who will have genetic analysis done on a panel of 35 genes known to be involved in various LGMDs as well as other muscle diseases with similar symptoms. The success of this initial phase will determine if the programme can be extended to include more patients in the US as well as internationally. Individuals with muscle weakness who suspect they may have a form of LGMD must take an online quiz to determine whether they are eligible for free genetic sequencing.

Online quiz

Eligible individuals who consent to participate will send a saliva sample for analysis and will receive a genetic report that they should take to their clinician for genetic counselling and proper disease management once the analysis is complete. It should be noted that some patients may not receive a genetic diagnosis through this programme if their causative mutation is in a gene not included in the selected gene panel.

The programme is sponsored by Cecil B Day Family, Inc (LGMD2B), Coalition to Cure Calpain 3 (LGMD2A), Jain Foundation (LGMD2B), Kurt + Peter Foundation (LGMD2C), LGMD2D Foundation, LGMD2I Fund (LGMD2I), and the McColl-Lockwood Laboratory.

Please contact the sponsoring organisations if you have any questions.

MYO-SEQ

MYO-SEQ
SEQUENCING GENETIC MUSCLE DISEASES

The second sequencing project will aim to sequence up to 1000 patients residing mainly in Europe with limb girdle weakness. MYO-SEQ will use a technique belonging to the DNA next generation sequencing techniques to test for all genes, rather than a select panel of genes.

Next Generation Sequencing (NGS) = DNA sequencing is any method used to determine the order of the bases within a strand of DNA. NGS is the catch-all term used to describe a number of different modern sequencing technologies. NGS, also known as high-throughput sequencing, allows sequencing of DNA much more quickly and cheaply than previously used methods.

The data from the Next Generation Sequencing will be fed back to the referring clinicians in the form of a research report. It will be the responsibility of the individual clinicians to carry out the appropriate tests to validate the results and provide their patients with a diagnosis.

Focusing on undiagnosed patients with a clearly defined clinical presentation (phenotype) will enable increased diagnostic rates for disease causing mutations in known genes in this patient group. Patients and samples will be identified by clinicians in the local clinical centres throughout Europe.

Engagement with private and not-for-profit funders has led to support for the MYO-SEQ project and a public-private partnership has been established.

You should speak to your clinician if you are unsure if you are participating in the MYO-SEQ project or if you would like to know more about it. You can also contact the Project Manager for MYO-SEQ, Dr Monica Ensini (monica.ensini@ncl.ac.uk).

LGMD2I patient network update

Earlier this year, an initial pilot study was run to test the "LGMD2I Patient Network", an online community where patients will be able to track their health and environment information in real time, with the goal of learning more about how LGMD2I impacts people's everyday lives and what can be done to improve the condition.

Six LGMD2I patients representing the whole spectrum of the disease (from a highly ambulatory child to an adult in a wheechair) participated in the pilot study. During one month, the participants input their data on several parameters, including hours of sleep, medications taken, number of falls, mood, etc. They also used a Fitbit device to capture their number of steps per day.

The study's main findings were: 1) there was a big variability between tracking adherence (those with a goal in mind had best adherence); 2) it's more efficient to track when there is a clear research question being asked; 3) automated tracking with a device like Fitbit is crucial to obtain data points in a consistent manner. These findings will now be used to design subsequent tracking experiments, with larger cohorts of patients.

This project is a collaboration between the LGMD2I Research Fund, the Samantha J Brazzo Foundation and Curious, Inc, an online platform for health tracking that is currently under development. The timeline for the next study will depend on the implementation of enhanced tracking features by the Curious portal, which are anticipated to happen by the end of the year.

Campaign for European year for rare diseases 2019

The European Year will send a strong political and public message on behalf of 30 million Europeans who suffer from a rare disease and will raise awareness and encourage researchers to focus on these rare, mostly unknown, seriously debilitating and often life-threatening diseases. Join the campaign and make 2019 the European year for rare diseases. Sign up now!

For more information see the Eurordis website

Meetings and events

Upcoming meetings

- ***Rare Disease Day*** – 28 February 2015, worldwide
  The main objective of Rare Disease Day is to raise awareness amongst the general public and decision-makers about rare diseases and their impact on patients' lives.

- ***Life without limits*** - 16-18 April 2015, Auckland, New Zealand
  Provides an opportunity for families affected by neuromuscular conditions, clinicians, researchers and allied health professional to get together, share progress and ideas and participate in informative breakout and training sessions. The conference theme is about empowering families through knowledge about the rare conditions they live with, supporting clinicians and researchers to make the best choices for their patients, who are often experts on their own condition.

Feedback on previous meetings

- Clinical conference, 31 October-1 November 2014, Norway
  A poster about the Global FKRP Registry was presented and also highlighted in a talk given by Prof Kate Bushby. The meeting was attended because the Scandinavian patient population is very important to have represented in the registry, as mentioned in the previous newsletter. We now have good links to the relevant clinicians within the neuromuscular network in Norway and we will work with them to raise awareness of the Global FKRP Registry over there.

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
Finland - finland@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

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