Global FKRP Registry Newsletter

www.fkrp-registry.org
www.treat-nmd.eu
www.lgmd2ifund.org
http://curecmd.org

Issue 2
April 2013

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

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.

If you have any questions or would like to contact us to give us any feedback, you can contact us directly by sending an email to:

coordinator@fkrp-registry.org

Welcome to the second Global FKRP Registry Newsletter!

What's inside?

1. Update on Registry Statistics

We now have 287 patients registered compared to the 187 patients from this time last year which again is fantastic progress! Last year we also told you that we had patients registered from 19 countries and this year we are very pleased to let you know that we have more than 30 countries represented. Germany, USA and the United Kingdom are still the most represented countries, but we have seen an increasing number of registrations from countries like the Islamic Republic of Iran and India. The map below (Figure 1) shows you at a glance the geographical coverage and the pie chart shows the percentage of patients from each country (Figure 2).

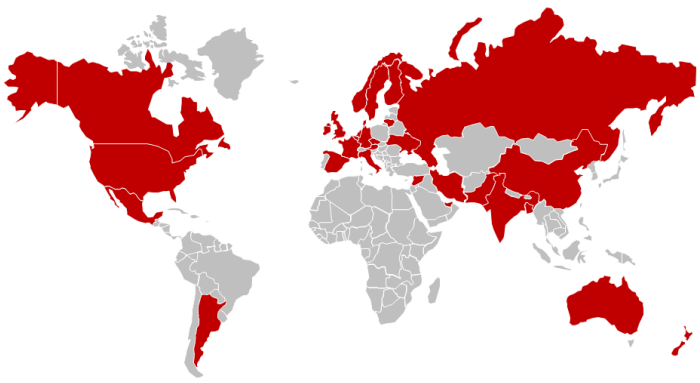


Figure 1. Map representing the geographical coverage of registered patients

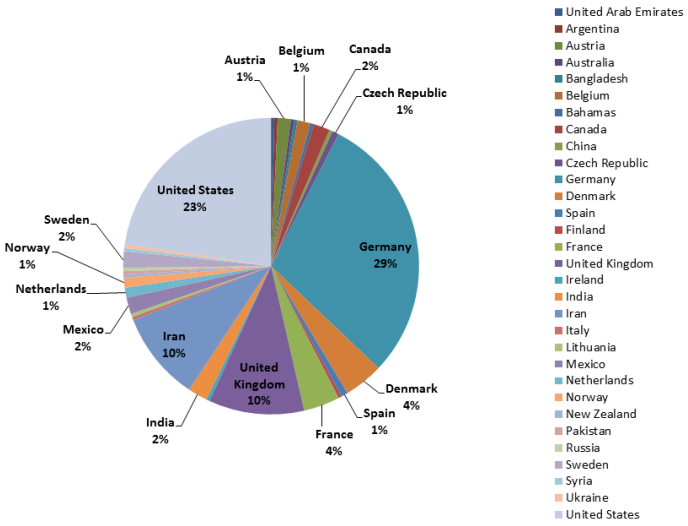


Figure 2. Pie chart showing the percentage of registered patients from each country

The most common diagnosis seen in the Registry is LGMD2I (60% of patients), with a gender ratio of 60:40 female:male, while MDC1C and other FKRP-related conditions represent the other 40% of the patients (20% each) with a gender ratio of 20:80 female:male, respectively (Figure 3).

**Please note that the actual numbers could be lower as there are several registrations that don't yet have a confirmed genetic diagnosis and may not indeed be related to an FKRP condition and so this number should be regarded with some flexibility.*

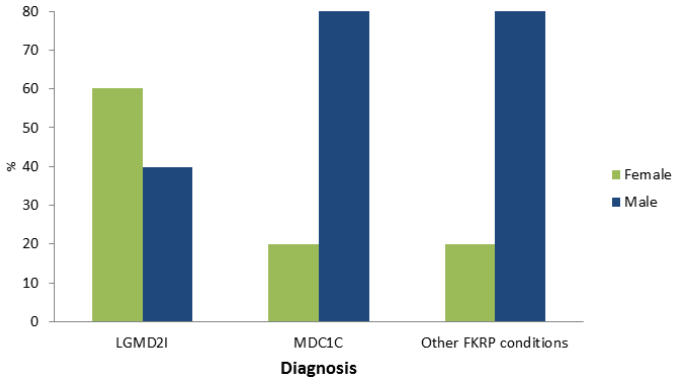


Figure 3. Ratio of females to males for each diagnosis

Preliminary analysis on patients with confirmed LGMD2I

A preliminary analysis was carried out for those patients that have information entered about which genetic mutation has caused their condition. The genetic mutations are only relevant to those patients with LGMD2I. The reason that only the data from these patients were used is because it is important know that the data being analyzed is from patients with a confirmed FKRP-related condition and to relate any clinical findings back to the genetic mutation which will help us to learn about the progression of these conditions. Some of the questions are answered by your doctor and so you may not recognize them. You are able to view all of the information entered about you (by yourself and your doctor) into the Registry by logging into your account.

Heart Function: Most patients have normal heart function (76%) with only 16% having started treatment due to impaired function, 4% have had deterioration and required a change in medication, while 4% have impaired function but are not requiring any medication yet (Figure 4).

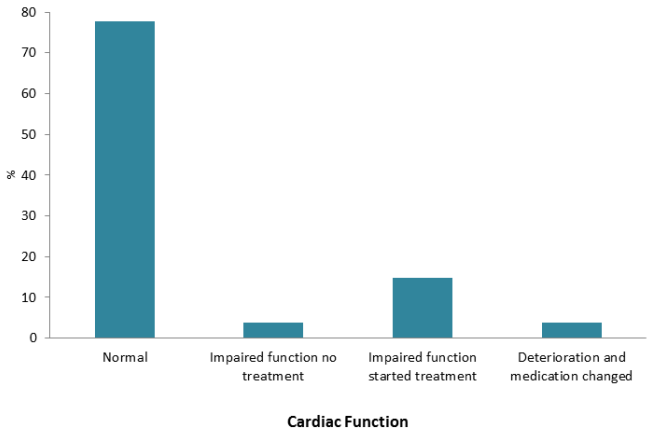


Figure 4. Graph to show patients' heart function according to latest cardiac check; Question: What was the last result of the cardiac check (ultrasound examination)?

Motor Function: Current motor function appears to be variable with a spread across the different categories, however most patients are able to walk (with and without support) and climb stairs with some assistance. Climbing stairs without assistance appears to be the only type of motor function that patients are not able to carry out (Figure 5). Only 6% of patients say they need to always use a wheelchair with 43% only needing to sometimes and 51% of patients not needing to use one at all (Figure 6).

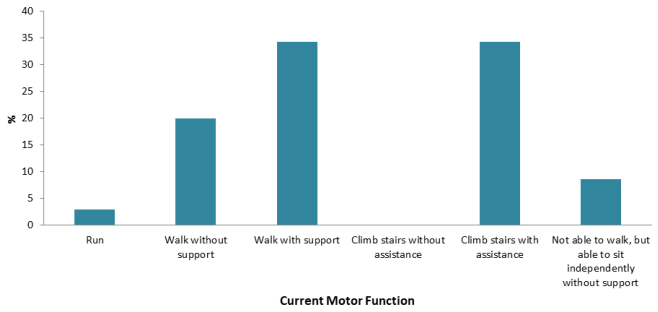


Figure 5. Graph showing patients' current motor function; Question: What is your current best motor function?

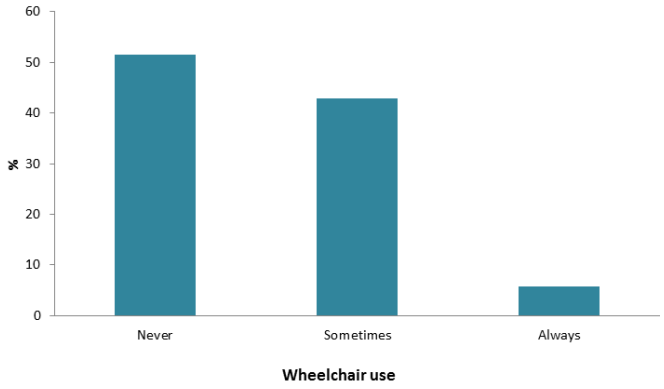


Figure 6. Graph showing current wheelchair use; Question: Do you currently use a wheelchair?

Muscle pain: Muscle aches and pain can be a common symptom of LGMD2I and the pie chart below shows that patients who get pain tend to get it the most after exercise and also at rest. However there are still 34% of patients that say they don't feel any aches or pains at all.

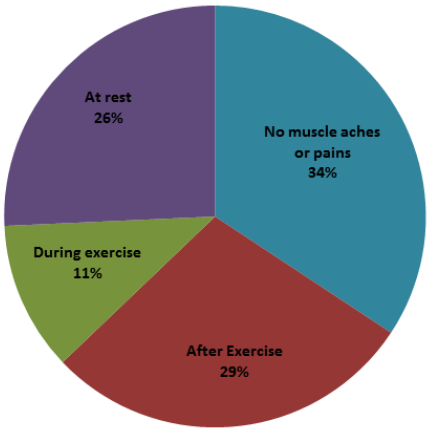


Figure 7. Pie chart showing when patients get muscle aches and pains; Question: Do you have muscle aches and pains (myalgia)?

Presenting symptoms: Knowing when the first presenting symptoms appear, and what those symptoms are, helps to inform doctors on the diagnostic pathway which will lead to earlier and more accurate diagnosis for patients. The bar chart below (Figure 8) shows that for most LGDM2I patients symptoms present below 20 years of age (total ~65%) with the most common symptoms (Figure 9) being weakness in the lower limbs, more specifically in the muscles closest to the center of the body, such as the upper leg muscles. HyperCKaemia, a raised creatine kinase level, is also observed fairly frequently but weakness in the hands and feet (distal weakness) is not observed, neither of which is any stiffness.

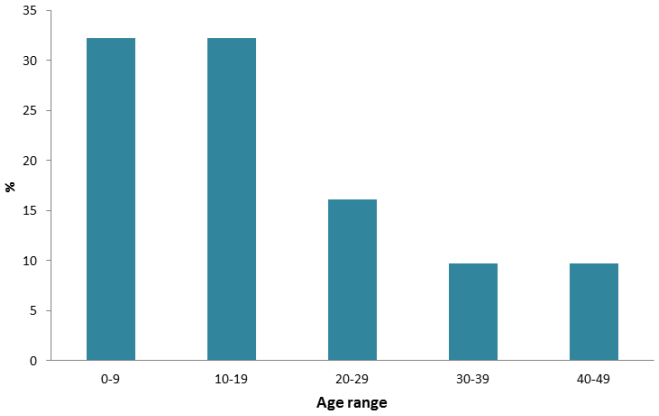


Figure 8. Graph to show the age range at which patients' presenting symptoms first appeared; Question: When were the first presenting symptoms?

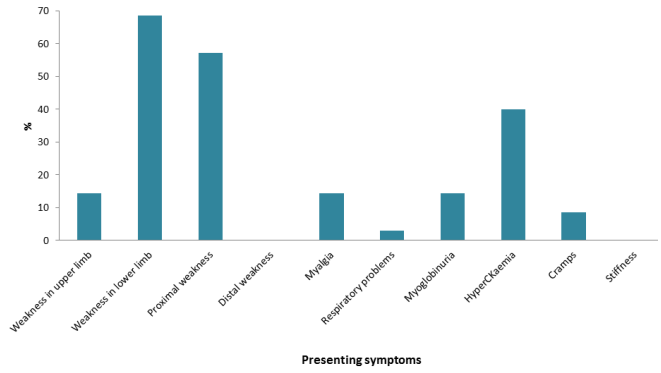


Figure 9. Graph to show the range of presenting symptoms that patients had (note: combinations of symptoms are observed); Questions: What were the presenting symptoms?

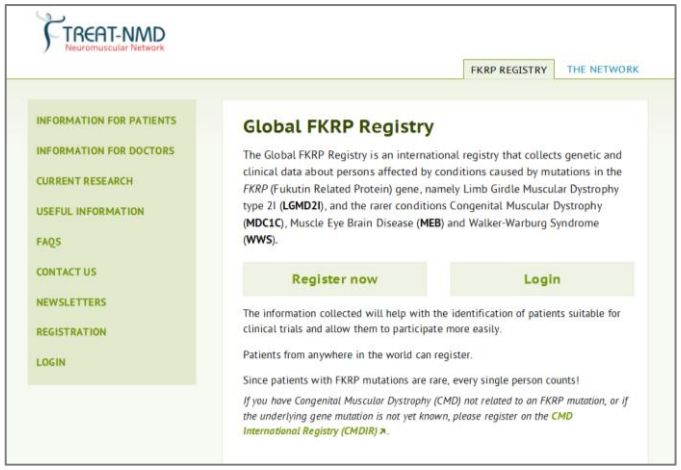
Complete datasets are essential for these types of analyses if any patterns and correlations are to be associated with the data. We hope to do further analysis on the data from the Registry and we will of course feed this back to you.

2. Website update

The Global FKRP Registry website has been undergoing some changes which you may have already noticed if you have recently logged in or just looked at the website. We have tried to add more information about the Registry including:

- why the Registry is important for not only finding patients for clinical trials but also for learning more about FKRP-related conditions;
- current research;
- FAQs, including information about the registration process and entering medical data into the registry;
- all newsletters.

We have also tried to make it easier for people to register and login by adding this function to the main homepage of the website.



Global FKRP Registry updated homepage

We will continue to work on the website and improve it but if you have any feedback in the meantime then we would love to hear it. You can **contact us** or your **national contact**.

You can see what information your doctor has entered about you when you log into your account. If they haven't yet input any data then next time you see your doctor in clinic make sure you ask them to do this. If you haven't yet chosen a doctor then either login in to your account and choose one from the list (which is being extended all the time) or if they are not listed then get just **contact us** and tell us who your doctor is.

3. New patient representative on the steering committee

We are very pleased to announce that Lacey Woods has joined the Global FKRP Registry Steering Committee as our first patient representative!
Lacey received her LGMD2I diagnosis in 2007 and has since then been gathering and providing accessible knowledge in layman's terms for others affected by LGMD2I. She has set up the LGMD2I website with the objective to educate and assist others with the disease, and she has also set up a Facebook group to help others find answers, provide support, and build friendships.

I'm sure you will all join me in wishing Lacey a warm welcome.

If you would like to contact Lacey then you can do so through the **LGMD2I website** using the contact page or via the **LGMD2I Facebook group** (you will need to be a member of Facebook to join the group).

4. Research Update

New grant to study mutant forms of FKRP

The LGMD2I Research Fund, the Samantha Brazzo Foundation and Cure CMD will jointly fund a research project to support drug screening on mutant forms of FKRP, in the search for compounds that restore normal protein function. It is still not well understood what the function of FKRP is as there have been very few studies that have focused on this protein. This project will try to better understand the role of the FKRP protein and try to find drugs that restore its normal function.

The project will be led by Dr. Sebahattin Cirak at the Children's National Medical Center and will use a novel approach for the analysis of mutated forms of FKRP and will allow for the identification of highly selective drug candidates that could be further tested in patients' cells and in mice models of FKRP deficiency. This project will help better understand the function of FKRP and could potentially lead to the discovery of therapeutic drugs against LGMD2I.

Developing New Antibodies for the Dystroglycanopathies

Antibodies are used by the body's immune system to identify and neutralize foreign objects such as bacteria and viruses. The antibody recognizes a unique part of the foreign object and allows the two structures to bind together with precision.

The project will focus on developing and characterizing antibodies that recognize normal and disease forms of alpha-dystroglycan. Existing antibodies can be challenging to use and give inconsistent results. This makes staining of the muscle for both diagnostic and research purposes difficult. This project is being carried out at two centers in the United Kingdom with Dr. Sue Brown in London, and Dr Glenn Morris in Oswestry.

Funding partners: LGMD2I Fund, Stevenson Family Fund at Cure CMD.

Developing AAV-miniagrin for testing in the FKRP mouse model

Mini-agrin is an engineered protein that helps muscle cells attach to their environment. In LGMD2I, as in some other muscular dystrophies, the attachment to the cell surroundings (called matrix) is flawed because of a defect in a protein called alpha-dystroglycan, causing the muscle to be more prone to injury. Data obtained in LGMD2I patient cells shows that mini-agrin restores normal function of these cells. The FKRP AAV-miniagrin project will test whether mini-agrin provides a benefit to the FKRP mouse model and should thus be further tested as a potential treatment for LGMD2I.

Funding partners: LGMD2I Fund, Samantha J Brazzo Foundation, Stevenson Family Fund at Cure CMD.

Development of two FKRP induced pluripotent stem cell lines (iPS)

iPS lines take blood cells and revert them back to an early undifferentiated cell type. This process is somewhat like time travel back in time for an individual cell, and creates a special cell (iPS) that can be directed to become brain cells (neurons, astrocytes), heart cells (cardiomyocytes) and skeletal muscle cells. This allows researchers to study these types of cells from people with a dystroglycanopathy to better understand how these cell types are impacted by the absence of sugars on dystroglycan, and to perform drug screening. This also opens up the door to genetically correct these cells, inject them into mice that have a dystroglycanopathy, and determine if the genetically corrected cells can "treat the disease" in the mouse.

This will be the first time that a stem cell therapy is tested in a mouse model of LGMD2I. If encouraging results are obtained, further testing will be done in order to bring this potential therapeutic approach to the clinic.

Funding partners: Cellular Dynamics, Inc, LGMD2I Fund, Stevenson Family Fund at Cure CMD.

Research completed in 2012

Characterization of the FKRPMD mouse model and testing of LARGE Over-expression (PI: Dr. Sue Brown). This 2 year project completed the characterization of this important dystroglycanopathy mouse model. Surprising results of LARGE over-expression, meaning increasing LARGE production early in development, will provide new insights and questions that need to be answered prior to pursuing this as a treatment target in the dystroglycanopathies. We look forward to Dr. Brown's publication of her work.

5. pro2i steroid trial update

Last year we told you about a proposed steroid trial in LGMD2I patients, which would be the first interventional trial for this population. The rationale was to test whether Prednisone will show an improvement in motor strength in patients with LGMD2I over a designated time period. The details of the study were still to be refined and submitted to an ethics board for review.

The study design and inclusion criteria for the trial have now been finalized and a draft protocol prepared, with the help of the Clinical Trials Centre in Freiburg, Germany. A summary of these are outlined below.

For information on the jargon used in clinical trials visit the **clinicaltrials.gov** website.

Study Design

Prospective multi-center phase II study including a 3 month double-blind randomized placebo controlled-phase followed by a 9 month open-label extension phase in which patients will receive prednisone or no treatment.

Patients will be randomised (distributed in a deliberately random way) to either receive treatment (prednisone) or no treatment (placebo) for 3 months (placebo-controlled phase) so that neither the patient nor the doctor (double-blind) will know what treatment the patient is receiving. Patients will then receive treatment for 9 months (open-label extension). Patients will be followed up for a maximum of 12 months (3 month double-blind phase, 9 month open-label phase).

A total of 17 centers are expected to participate across 8 countries (Denmark, France, Germany, Netherlands, Norway, Sweden, UK, USA).

The inclusion criteria is the individual criterion, or standards, set out for a study and is used to determine whether a person can participate in that study. Inclusion criteria help to identify suitable participants for a study and often include gender, age, type of disease, treatment history and medical conditions.

Inclusion Criteria for pro2i:

1. Clinical and molecular diagnosis of LGMD2I (confirmed mutation in the FKRP gene);
2. Male and female patients aged >18 years;
3. Able to swallow oral tablets;
4. Ability to walk at least 150 meters in 6 minutes;
5. Perform the timed up and go (TUG) test in >7 seconds and <50 seconds;
6. Written informed consent obtained according to international guidelines and local law;
7. Ability to understand the nature of the study and the consent form and to comply with study related procedures.

There are also a number of exclusion criteria that would exclude some patients from the trial if any of these are met.

The Registry would be one of the methods used to find potentially eligible patients for this study.

When we have more information about the pro2i study we will let you know.

6. Family conferences and events

- ***Congenital Muscle Disease Family Conference***

  This is a great event where medical professionals will come together with families to discuss updates in treatments, issues facing the CMD community, as well as a chance to bond with other families.
  14-15 July 2013
  Bethesda, Maryland, USA

- ***Dystroglycanopathies Patient and Family Conference***

  The conference focuses on the basics of the dystroglycanopathies, research updates, and provides opportunities to network with clinicians, researchers and other patients and families.
  19-21 July, 2013
  Iowa City, Iowa, USA

- ***EMBO Workshop on Molecular Mechanisms of Muscle Growth and Wasting in Health and Disease***

  This meeting will focus on the molecular mechanisms involved in muscle wasting diseases including cachexia, sarcopenia and muscular dystrophies. Its focus on disease aspects in skeletal muscle, its interactive format and its small size makes this meeting unique.
  15-20 September 2013
  Monte Verita, Ascona, Switzerland

- ***World Muscle Society Congress***

  The symposium will be in the traditional WMS format with 3 selected topics: Myometrix in Health and Disease; Immunity and Muscle Disease; Advances in Therapy for Neuromuscular Disorders; Contributions will also be welcome on new advances across the neuromuscular field. One day of the symposium will be dedicated to each of the selected areas. Invited keynote speakers will summarize the state of the art on the selected topics, covering clinical, molecular and other aspects.
  1-5 October 2013
  Monterey, California, USA

- ***Muscular Dystrophy Campaign 2013 National Conference***

  The conference will provide information on a wide range of neuromuscular conditions, including research news and workshops which will be led by a clinician and a neuromuscular advisor.
  12 October 2013
  East Midlands Conference Centre, Nottingham, UK

- ***Rare Disease Day***

  For more information on events happening locally visit the rare disease day website: http://www.rarediseaseday.org/
  28 February 2014

If there are any specific topics that you would like to see covered in the next newsletter then please get in touch.

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