Global FKRP Registry Newsletter

Issue 3
December 2013

www.fkrp-registry.org

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 third Global FKRP Registry Newsletter!

What's inside?

1. Care recommendations for FKRP-related muscular dystrophies

Patients with neuromuscular diseases require a multidisciplinary approach and the level of care and treatment given should be universal. Although there are currently no standards of care that have been developed specifically for the diagnosis and management of FKRP-related muscular dystrophies (LGMD2I, MDC1C, muscle eye brain disease, Walker-Warburg Syndrome), the following recommendations apply generally to patients with muscular dystrophy.

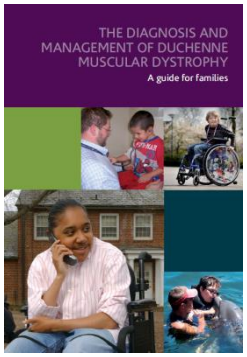
Standards of care specify appropriate management and treatment of a disease based on scientific evidence and/or collaboration between medical professionals.

Severely affected LGMD2I patients have a phenotype that is similar to Duchenne muscular dystrophy (DMD), which means that the current standards of care for DMD can be applied to the management of LGMD2I.

Where "genotype" is the genetic makeup, the "phenotype" is the genetic and environmental influences that come together to create a person's physical appearance and behaviour.

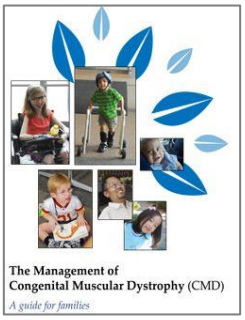
The standards of care for DMD were originally published in an academic journal, Lancet Neurology, and then a guide for families was subsequently developed in lay language to allow families to understand the medical terminology and discuss their own specific needs with their healthcare provider.

- ***Standards of care for the diagnosis and management of DMD – academic article***
- **Family guide for the management of DMD**



Separate guidelines have also been developed for the management of the congenital muscular dystrophies (CMD), including MDC1C. Again an academic article was produced and then a family guide was developed.

- ***Consensus Statement on Standards of Care for Congenital Muscular Dystrophies – academic article***
- ***Family guide for the management of congenital muscular dystrophies***



The Global FKRP Registry collects clinical and genetic information about patients with FKRP-related muscular dystrophies and asks that this information is updated annually. By collecting all of this information it can help us to understand the natural course of disease progression over time (natural history) which will help to inform the development of treatment guidelines and standards of care specifically for FKRP-related muscular dystrophies.

There are certain aspects of the care standards for DMD and the CMDs worth highlighting, including recommendations for looking after your heart and lungs, and maintaining good bone health, which are relevant to the FKRP-related muscular dystrophies.

There are several ways in which guidelines can be produced to form standards of care, and these can either be consensus based or evidence based.

1.1 Regular heart and lung check-ups

It is important to have regular check-ups on how your heart and lungs are functioning. Even if the latest results show that there has been no deterioration it is still important to have regular screening checks as this will pick up on any issues before they become serious problems. If you have never had a check-up for your heart and/or lungs then you should discuss this with your doctor.

For anyone who has never had these types of tests before, a description of what is involved with both heart and lung function tests are described below.

Check-ups for the heart

Recommendations for LGMD2I:

A cardiac investigation (heart check) should occur at diagnosis, every two years to age 10, and annually thereafter.

LGMD2I may lead to an enlarged heart which will register on an echocardiogram as an abnormal ejection fraction (see below for more information about echocardiograms). An enlarged heart can be treated with medication but not everyone with LGMD2I will develop an enlarged heart. People with LGMD2I may experience a drop in their ejection fraction prior to experiencing progressive muscle weakness.

Patients with heart issues can be treated with medication, such as angiotensin-converting enzyme (ACE) inhibitors and beta blockers.

- ***Family guide for the management of DMD***

Recommendations for the congenital FKRP-related MDs (MDC1C, Muscle eye brain disease, Walker-Warburg Syndrome):

Heart function should be checked at diagnosis and then annually thereafter due to the increased risk of developing cardiomyopathy (a disease of heart muscle that causes enlargement of the heart and rigidity of the walls of the heart).

Children with signs of cardiomyopathy can be treated with medications such as angiotensin-converting enzyme (ACE) inhibitors and beta blockers. The management of severe cardiomyopathy or heart failure in children with FKRP-related muscular dystrophies is no different than in the general paediatric population.

- ***Family guide for the management of congenital muscular dystrophies***

Types of investigations:

Heart issues are checked with an echocardiogram, an ultrasound of the heart. An echocardiogram can take about 30-45 minutes. A clear gel is placed over the left side of the chest which allows the sensor to have better contact with the skin. The sensor is then held firmly

against the skin as it is moved across the chest. Pictures of the inside of the heart will be displayed on the screen.

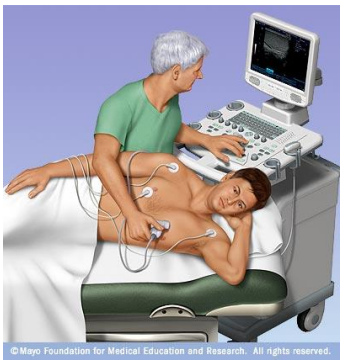


Image 1. Echocardiogram procedure (Ref. Mayo Foundation for Medical Educations and Research)

An echocardiogram measures heart movement, size and how well the heart is pumping. A normal ejection fraction, while reassuring does not mean the heart should not be evaluated annually. The ejection fraction on an echocardiogram should be trended to ensure optimal management.

Check-ups for the lungs

Breathing problems are common in FKRP-related muscular dystrophies and assessment and treatment of respiratory failure should be performed in parallel with heart investigations.

Recommendations for LGMD2I:

Whilst a person is still walking then minimal assessment of breathing function is required, such as annual measurement of forced vital capacity (FVC, see below for more details). Assessment of breathing function becomes more important when someone loses the loss of independent walking. Frequency of assessments will depend on the stage of the condition and breathing function but at a minimum it is recommended that FVC measurement is carried out at least every 6 months once independent walking stops.

It is recommended that FVC (in % predicted) in the sitting position should be performed annually. When FVC is abnormal (<80%) an additional measurement in the lying down position should be performed to detect potential diaphragm weakness.

- ***Family guide for the management of DMD***

Recommendations for the congenital FKRP-related MDs (MDC1C, Muscle eye brain disease, Walker-Warburg Syndrome):

Depending on the degree of weakness, such as with WWS, respiratory support may be required from birth. This makes it very important for children with FKRP-related MDs to be evaluated before symptoms are seen. There are many preventative methods that can be used to ensure that children maintain good breathing function.

In patients less than 5 years old in whom FVC cannot be measured, another test such as pulse oximetry, should be performed to determine breathing function. Again, this test should be performed annually.

- ***Family guide for the management of congenital muscular dystrophies***

Types of investigations:

Forced vital capacity (FVC) measures the amount of air that can be blown out in one breath, which determines lung function. A spirometer is the name of the device used to measure FVC.

Image 2. FVC procedure (Ref. Mayo Foundation for Medical Education and Research)

Firstly, the patient will breathe in fully and then seal their lips around the mouthpiece of the spirometer, before blowing out as fast and as far as they can, until their lungs are completely empty. This can take several seconds. They may also be asked to breathe in fully and then breathe out slowly as far they can. A clip may be put on the nose to make sure that no air escapes through the nose. The measurements may be repeated two or three times to check that the readings are much the same each time.

Assessing breathing status is best done through annual pulmonary function testing (PFTs). During PFTs a person is asked to do several different breathing manoeuvres, including a FVC. In PFTs, it is the FVC and FVC% predicted that is the important value to follow over time. A single normal value while reassuring does not mean there is not a need for annual evaluation. Breathing issues, if present, are progressive, hence the need for trending. Not all individuals with FKRP-related muscular dystrophies will have breathing problems as there is a range in clinical severity. Breathing issues typically only become a problem when muscle weakness leads to difficulty in walking. If FVC% predicted is abnormal (typically less than 60%) a sleep study may be recommended to evaluate whether breathing

support is needed in sleep. Thus, FVC% predicted is solely a screening test to look for a degree of breathing impairment that then needs to be further evaluated with a sleep study. Breathing issues can be treated with breathing support.

- ***Guide to respiratory health in neuromuscular disorders produced by Muscular Dystrophy Canada***

1.2 Bone health

Bone health is important in both patients who are walking, and also those that have stopped walking. Due to lower bone mineral density, patients with an FKRP-related muscular dystrophy are at an increased risk of fractures (broken bones) compared to the general population. The major underlying factors for poor bone health are: decreased mobility, muscle weakness and steroid therapy.

A broken leg can be a significant threat to the continued ability to walk. Treatment with surgery should therefore be considered to allow patients to get back up on their feet as quickly as possible. If a person with an FKRP-related muscular dystrophy who is still walking breaks their leg, the recommendation is that internal fixation (surgery to stabilize the break as quickly as possible) is needed to resume walking and to have the greatest chance to maintain walking.

Steroid treatment is known to add to the risk of low bone density. Bone density may need to be assessed with blood tests, bone scans and other X-rays. This is still an area where further research is needed to establish best practice.

- ***Family guide for the management of DMD***

1.3 Flu vaccinations

Flu is a contagious and serious disease especially for those affected by a neuromuscular condition. People with muscular dystrophy, like LGMD2I, are classed as high risk for developing flu-related complications if they get sick from influenza.

- ***Information from the Centers for Disease Control and Prevention (CDC)***
- ***Information from the NHS***
- ***Information from the World Health Organization (WHO)***

In general, it is recommended that anyone with a muscular dystrophy gets a flu vaccination because these individuals are at an increased risk of serious complications from flu. It is important that those individuals stay informed and take steps to protect themselves and their families.

Current guidelines recommend that all children and adults with an FKRP-related MD receive the flu vaccination annually.

You should always check with your doctor before obtaining any vaccination, especially if you are taking immune-suppressing medications such as corticosteroids (i.e. prednisone, prednisolone, deflazacort).

The nasal flu spray vaccination is not recommended for anyone on corticosteroids.

2. Global FKRP Registry Statistics

The total number of patients registered to date is 278, which is lower than the figure quoted in April due to the confirmation since then that some registered patients did not have an FKRP-related muscular dystrophy. Of the 278* registered patients, 47% are male and 53% are female.

The most common diagnosis reported in the registry is still LGMD2I (92% of patients, 60:40 female:male), with the remaining patients reported as having either MDC1C (5% of patients, 20:80 female:male) or another FKRP-related muscular dystrophy (3% of patients, 50:50 female:male) (**Figures 1 & 2**).

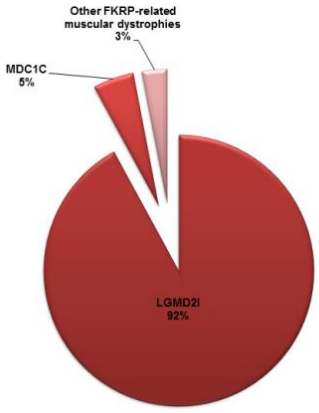


Figure 1. Pie chart showing the representation of each diagnosis as reported by patients

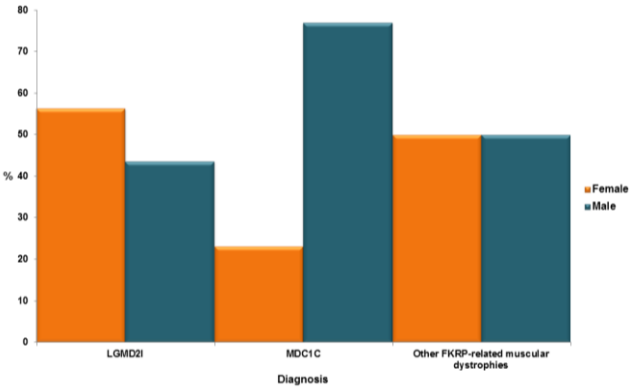


Figure 2. Ratio of females to males for each diagnosis

The current age range that represents the most patients is 40-49 years, with the youngest and oldest patients in the 0-9 years and 70-79 years age range, respectively (**Figure 3**).

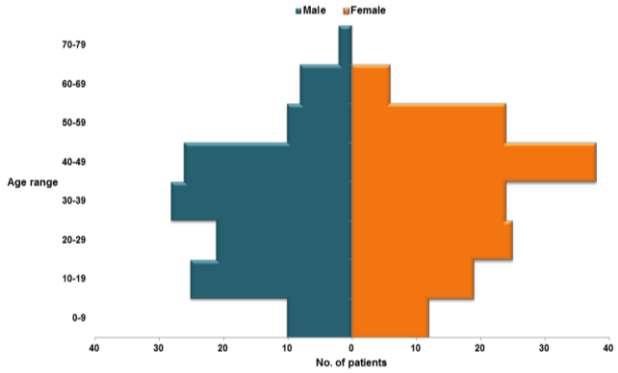


Figure 3. Age range of registered patients for males and females

27 countries are currently represented in the registry (**Figure 4**) with the majority of patients still being from Germany (34%), USA (26%) and the United Kingdom (14%).

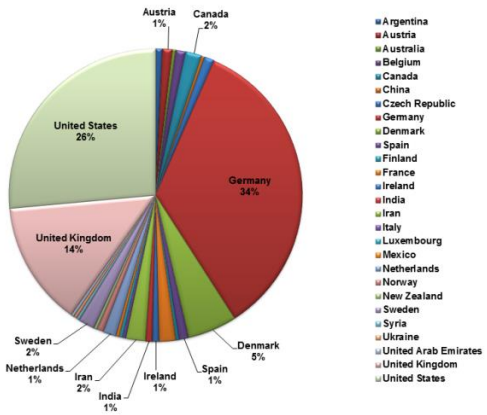


Figure 4. Pie chart showing the percentage of registered patients from each country

The number of patients registering since the registry launched in April 2011 has been fairly steady across the three years: 112 patients in 2011, 82 patients in 2012 and 84 patients in 2013 to date (**Figure 5**).

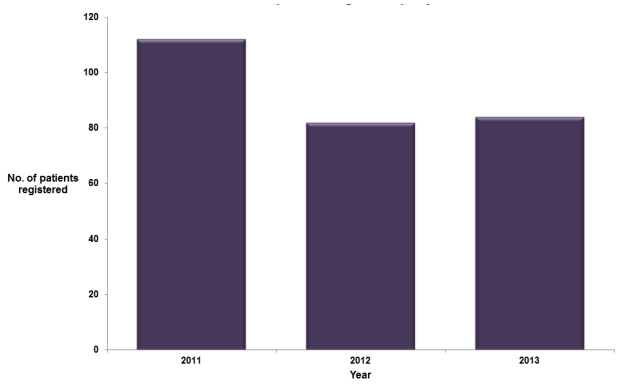


Figure 5. Number of patients that have registered per year

** Not all of these patients have been genetically confirmed as having the condition they have reported.*

3. LGMD2I Patient Network

The "LGMD2I Patient Network" is an online portal where patients will be able to track their health and environment information in real-time, as a community. This can be done in an anonymous way, providing data towards the aggregate data from the population as a whole, or patients can choose to share their profile with the portal community. LGMD2I is a highly variable disease with patients showing very different functional ability regardless of the underlying genetic mutation. By sharing data through the portal it will provide a better understanding of the natural progression of the disease whilst linking it to any relevant environmental factors.

It is hoped that the portal can be linked to the Global FKRP Registry to allow a comparison to be made with the genetic information.

A funding application for the portal has been submitted to the Patient Centered Outcomes Research Institute (PCORI) and a response is expected later this month. The application has been made in collaboration with the LGMD2I Research Fund, Curious, Inc (an online workspace for tracking, querying and sharing personal data, and the organisation that will be responsible for building the LGMD2I Patient Network Platform), Samantha J Brazzo Foundation, Cure CMD and the LGMD2I Patient Network Steering Committee, which includes Lacey Woods, a patient diagnosed with LGMD2I, and who is also a member of the Global FKRP Registry Steering Committee.

Curious is currently interviewing patients and gathering feedback to build an initial pilot study that will launch the Network. Once the pilot study is completed and the patient feedback incorporated, the Network will be open to the entire LGMD2I patient community. For more information on the portal or if you would like to participate in the pilot study, please contact Dr Claudia Mitchell at **claudiam@lgmd2ifund.org**.

4. pro2i steroid trial update

In the last newsletter (Issue 2, April 2013) we told you that the protocol for the pro2i trial - clinical trial to test whether Prednisone shows an improvement in motor strength in patients with LGMD2I - had been finalised.

We are now aiming to bring together a group of possible funders which would jointly fund the trial and we will of course inform you when we know more.

5. Research update

Development of Mouse Models for FKRP

Previously reported work on the characterisation of new mouse models for FKRP has been published in the academic journal Human Molecular Genetics. This work was supported in part by Cure CMD.

The paper describes two mouse models. The first (FKRPMD), replicates the progression and pattern of muscle weakness which is seen in limb girdle muscular dystrophy, which may allow it to be used in the testing of potential therapies. The FKRPMD model has also been crossed with one that overexpresses LARGE (like-acetylglucosaminyltransferase), a gene involved in the glycosylation of alpha-dystroglycan. Surprisingly, overexpression of LARGE results in a worsening of the muscle pathology implying that any future strategies based upon LARGE up-regulation requires careful management. It is still unclear if postnatal overexpression of LARGE will have the same deleterious effects.

- ***Link to academic journal***

6. Conferences and events

- **Rare Disease Day**

  For more information on events happening locally visit the rare disease day website.
  28 February 2014

- **Muscular Dystrophy Association (MDA) Clinical Conference**

  MDA is committed to enhancing the communication of new research findings and of information relating to the delivery of effective medical care for neuromuscular diseases. To achieve this goal, MDA hosts an annual conference series, with scientific and clinical conferences held in alternate years.
  16-19 March 2014
  Chicago, Illinois, USA

- **World Muscle Society Congress**

  The symposium will be in the traditional WMS format with 3 selected topics: Limb girdle muscular dystrophies; protein aggregation, autophagy and proteomics; and advances in therapy for neuromuscular disorders.
  7-11 October 2014
  Berlin, Germany

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.