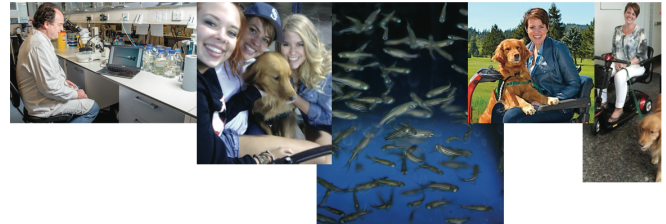




# Newsletter

## 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 6<sup>th</sup> Global  
FKRP  
Registry Newsletter!

What's inside?

Global FKRP Registry statistics

Steering Committee - update

Patients' stories

Research updates

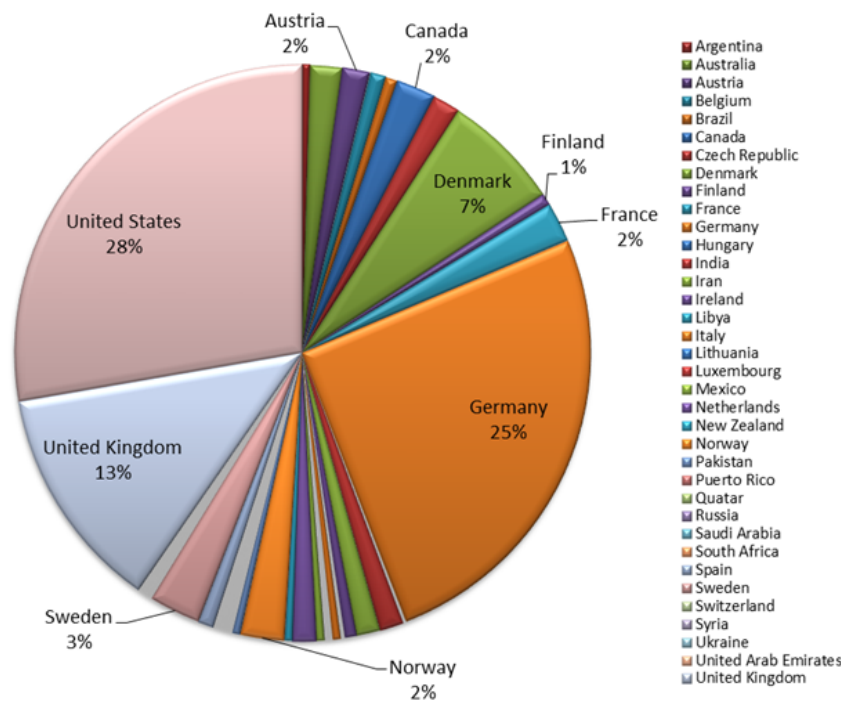
Clinical studies

International collaboration and  
trial readiness for LGMDs

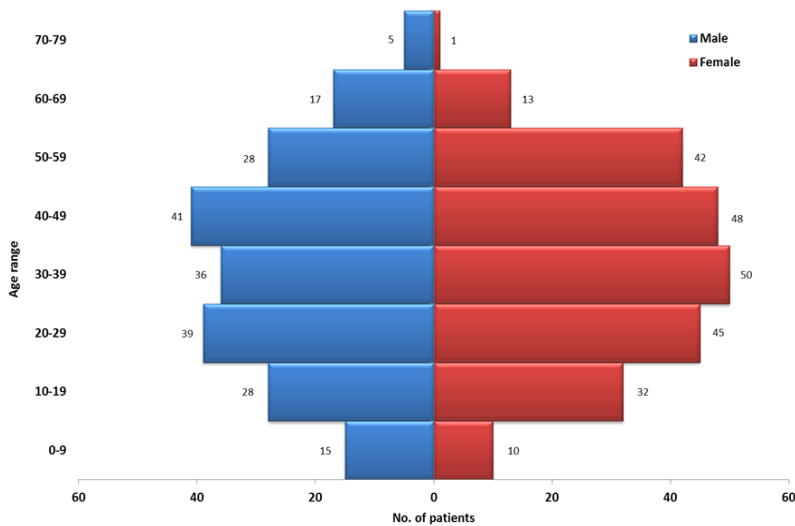
Meetings and Events

## Global FKRP Registry statistics

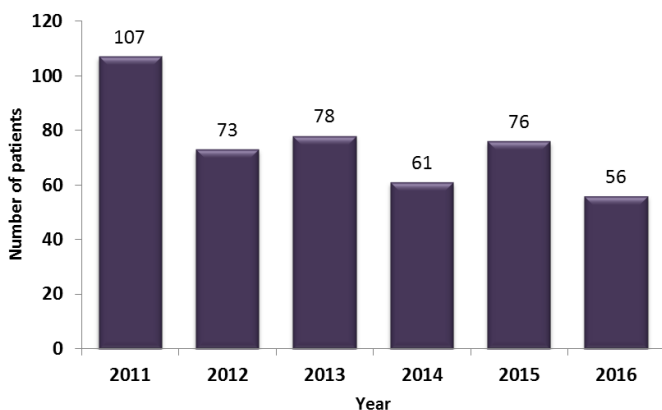
There are 451 patients registered, of which 241 are female and 210 are male, from 36 countries (**Figure 1**).



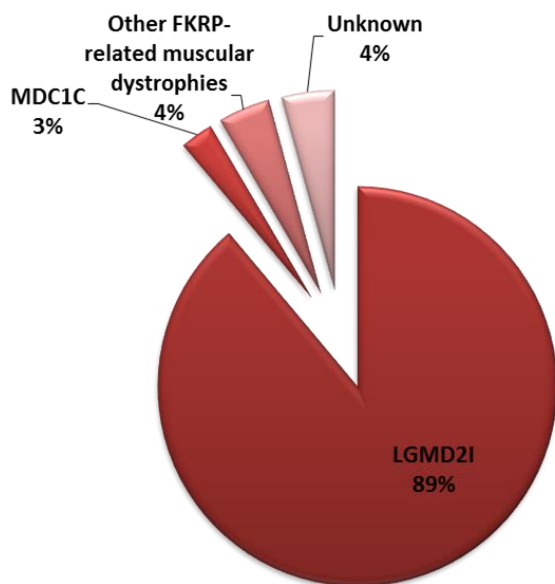
**Figure 1.** Pie chart showing the percentage of registered patients from each country.



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



**Figure 3.** Number of patients that have registered per year



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

USA (28%), Germany (25%), and the UK (13%) represent the largest number of patients. The Scandinavian countries are still under-represented in the registry. However, the numbers of registrations from Denmark have nearly doubled since the previous newsletter ([Issue 5](#)).

The median age range for people on the registry (both male and female) is 30-39, with the range of ages spanning from 0-9 to 70-79 years (**Figure 2**).

**Figure 3** shows the year on year recruitment numbers. The numbers may differ from what was reported in previous newsletters and this is 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.

The most commonly reported diagnosis is LGMD2I (89%) with the remaining patients reported as having MDC1C (3%), another FKRP-related MD (4%) or the diagnosis is unknown. (**Figure 4**).

This shows how important it is for us to have a copy of your genetic report.

A genetic report (also known as molecular report or DNA laboratory report) or a confirmation in a clinical letter from your doctor provides information about your condition and also the specific mutation that is causing the condition. This information is needed to confirm if you could be eligible to be included in a clinical trial or research study when those take place. All you need to do is send a copy to us and we can enter the information into the registry for you.

## Genetically confirmed patients

The Global FKRП 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 know the specific mutation causing the condition. We are still awaiting confirmation of genetic diagnosis from a number of patients and at present we can only say for certain that 210 patients in the registry definitely have an FKRП-related MD.

Out of the total number of patients who have been confirmed as having an FKRП-related MD 112 are female and 98 are male, and these represent 19 different countries. 99% of these patients have LGMD2I, 1% MDC1C (Figure 5). The median age range is 40-49 years and the oldest patients are in the 70-79 years age range (Figure 6).

When looking at genetic conditions there are various important factors – one of them is family history. Through the registry, we have asked if you know any family members affected by an FKRП-related MD. Out of those who are genetically confirmed as having an FKRП-related MD 26% said that they did have a family member also affected by an FKRП-related MD, and 72% said that they didn't know of any family members who were affected (Figure 7).

### LGMD-diagnosis.org

Several LGMD family foundations have partnered to offer free genetic testing for patients affected by various forms of LGMD to obtain a specific genetic diagnosis. Currently the free genetic testing is offered to those living in the US, but it is hoped to eventually expand internationally.

Patients in other countries are encouraged to take the eligibility quiz at [lgmd-diagnosis.org](http://lgmd-diagnosis.org), so that they can be contacted quickly if the programme expands and free genetic sequencing is offered internationally.

Please visit [lgmd-diagnosis.org](http://lgmd-diagnosis.org) for more information and to take an online quiz to determine if you are eligible for free genetic sequencing.

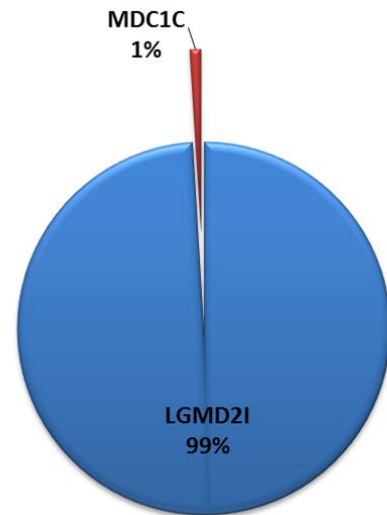


Figure 5. Pie chart showing the representation of each diagnosis as reported by patients.

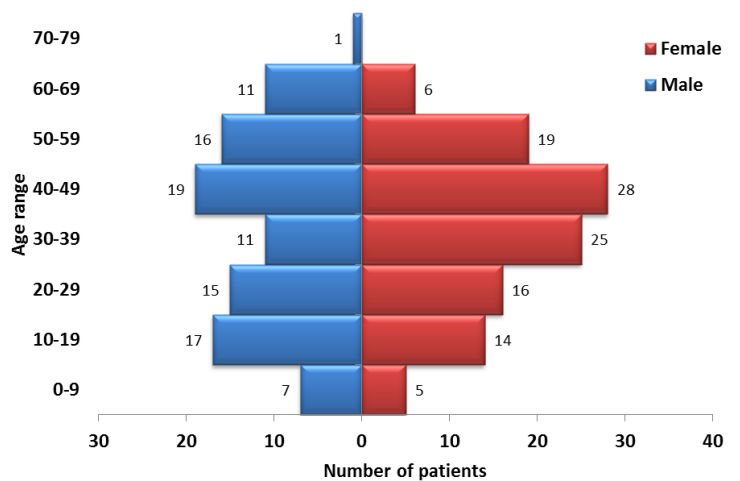


Figure 6. Age range of registered patients for males and females, for all genetically confirmed patients

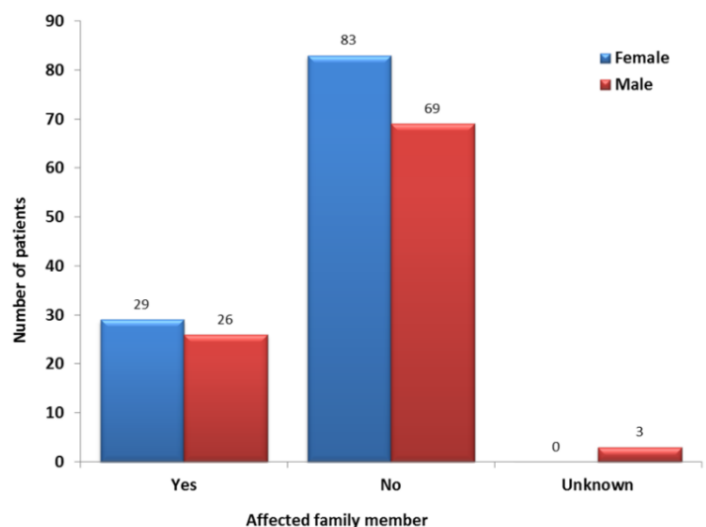


Figure 7. Number of patients with affected family members by male and female, for all genetically confirmed patients.

## Steering Committee – update

Dr Anne Rutkowski, a Co-founder and a Former Chairman of Cure CMD, has stepped down from the Global FKR Registry Steering Committee. We would like to thank Anne for her invaluable contribution to the Global FKR Registry over the years and we wish her all the best for the future.

Anne will be replaced on the Committee by Dr Herb Stevenson. Herb is a Sports Medicine Physician and Associate Professor at the University of Massachusetts Medical School. He is the father of a son with LGMD2l. Herb has worked since 2011 with Cure CMD through the Stevenson Family Fund to support research in congenital muscular dystrophies. He has an interest in muscular disorders and has helped work with scientists and clinicians to advance research with a particular focus on translating gene therapy for congenital muscular dystrophies into clinical trials. Herb resides in Massachusetts with his wife Meredith and 3 children Hannah, Amelia, and Carter. Herb will join the existing seven members of the [Global FKR Steering Committee](#).

I am sure you will join us in wishing Herb a warm welcome.

## Patients' stories

We would like to share with you patients' stories through the registry website and the newsletter. Please [get in touch](#) with us if you would like to share your story with us.

In this issue of the newsletter we have a new story.

### "Standing tall" by Lindsay Mullins

My life has been a very active life, until recently. I have been extremely active in all sports with an active social and travel focus throughout my life.

School age: Running, cricket, Aussie rules, swimming, tennis, cycling, squash, abseiling, hiking etc. Always able to do every task, and although always a slow runner, and never very strong, was able to participate, compete and enjoy without ever realising that something might have been a problem.

Twenties/Thirties: Travelled extensively, hiking in Europe and throughout Australia. Played a lot of social sports, and achieved high standard at tennis, amongst many other activities, again showing no sign of physical weakness.

Forties: Early to mid-forties still played competitive tennis, swimming, cycling, travelling, and started a family. No signs until late forties when I started running for fitness. Had quite a strange running gait, and an upright running posture, but I thought it was due to bad knees and a bad back because of the excessive contact sport when I was younger [...]

About 4 years ago I was struggling to bend down and stretch at all and so I took up Pilates, and it was through the physiotherapist that advised I should get some specialist testing for the muscle weakness...

Read the full story on the [registry website](#).

### Update on further work on mouse models for FKRPs

Preclinical research is a key step in the development of new disease treatments. Most frequently, a potential therapeutic approach will only be tested in patients once it has been shown to be effective in an animal model that reliably reflects human disease. The choice of an appropriate animal model is crucial for that. We have been regularly updating you on developments with mouse models for FKRPs and you can find previous updates on the registry website [here](#).

The recent study carried out by the Danish group from the University of Copenhagen contributes additional knowledge about the mouse models.

The main findings from this study are that the mouse model FKRPs L276I (with a common homozygous L276I mutation) created by this group shows a slowly progressing disease resulting in muscular weakness (myopathy), which resembles that in patients with LGMD2I who have a homozygous L276I mutation. The researchers have also created another model – a hemizygous FKRPs L276I mouse, which resembles the homozygous FKRPs L276I model at comparable ages. They also attempted to create a mouse model with no FKRPs (an FKRPs knock) but it was not viable, which was consistent with previous findings.

The mouse models developed by this group emphasize the significance of FKRPs in glycosylation of alpha dystroglycan. They could also prove valuable as a late onset model for LGMD2I and could be used for studies of disease progression as well as for developing feasible therapies for late onset myopathies.

❖ [Link to the academic journal](#)



### Cardiac involvement in patients with limb girdle type 2

A recently published article in the *International Journal of Cardiology* presents the results of a 9 year follow-up study of 100 LGMD2 (types A-L) and 30 Becker muscular dystrophy (BMD) patients. The study aimed at assessing the degree and progression of heart (cardiac) involvement in those groups of patients.

Cardiac involvement in BMD and LGMD2 may vary substantially, however this 9-year follow study showed that Left Ventricular Fraction of Ejection (LVFE), a measurement of the percentage of blood leaving your heart each time it contracts, decreased significantly in patients with BMD and LGMD2I.

Additionally, the majority of patients with LGMD2E had a form of heart problem (left ventricular systolic dysfunction) which results in the heart being unable to pump out as much blood as a normal heart would be able to. This causes more blood to remain in the lower heart chamber (ventricle).

These findings point towards the need for a tailored cardiac screening and a timely follow up according to genetic subtypes, with particular cardiac investigations of patients with BMD and LGMD types 2I and 2E.

The findings support the previously discussed recommendations ([newsletter3](#)) for regular check-ups for the heart in LGMD2I.

❖ [Link to the academic journal](#)



## Research updates

### A new potential function of FKRP in glycosylation process

FKRP is one of the currently 18 known genes that can lead to an alpha dystroglycan related dystrophy ( $\alpha$ DG-RD, dystroglycanopathy). The study carried out by the group of researchers in Japan expands our knowledge of the complex and still not fully understood glycosylation mechanism.

The researchers show that ribitol 5-phosphate (Rbo5P) is a rare sugar unit (glycan) in mammals and that alpha-dystroglycan ( $\alpha$ DG) requires two of these units to function. FKRP is involved in the attachment of Rbo5P to dystroglycan (glycosylation). The study in cells also suggest that the formation of the ribitol 5-phosphate (Rbo5P) requires cytidine diphosphate ribitol (CDP-Rbo) and by adding CDP-Rbo to the cell culture the attachment of Rbo5P to dystroglycan (glycosylation) was improved. The results of this study provide an additional insight into the role of FKRP in glycosylation process and raise the possibility of the supplementation of CDP-Rbo as a potential therapeutic strategy in alpha dystroglycan related dystrophies. More studies using animal models will be required to explore this further.

❖ [Link to the academic journal](#)

## Clinical and observational studies

### FKRP registry used for recruitment

An observational study involving LGMD2I patients is currently being conducted in the United Kingdom. The purpose of this study is to collect information using MRI scans to better understand why some patients with Duchenne Muscular Dystrophy have learning or behavioural difficulties. This study is taking place in the United Kingdom and is sponsored by Muscular Dystrophy UK.

The study includes various groups of patients: people with DMD, people with Limb-Girdle Muscular Dystrophy and healthy volunteers (people not affected by a muscle wasting condition). People with LGMD are involved in this study as a control group because the researchers want to compare the results from Duchenne Muscular Dystrophy patients with people who have a similar muscle condition. The control group will help with the analysis of how specific the findings are to the missing dystrophin in Duchenne muscular dystrophy.

The researchers have approached the Global FKRP Registry for help with the recruitment for this trial. The study recruits boys and men (aged 8-30) with LGMD2I who live in the UK. The patients who are registered with the Global FKRP Registry and who are potentially eligible for participation in this clinical study as a control group have been contacted. For more information about the study, please visit the [Muscular Dystrophy UK website](#).

### Myostatin inhibitor study to be conducted in LGMD2I patients

A new trial for ambulatory adults with LGMD2I is being initiated at Kennedy Krieger Institute in Baltimore, Maryland, USA. This study is carried out in collaboration with Pfizer. This is a phase 1b/2 open-label multiple ascending dose study.

The aim of the study is to determine the optimal safe and effective dose of the drug called PF-06252616 in LGMD2I patients. It is an open label study, which means that the clinicians and participants know which therapy is being administered.

The PF-06252616 is a neutralizing antibody to myostatin. Myostatin is involved in the regulation of the muscle growth, and the inhibition of myostatin has shown increased muscle mass and strength in laboratory animals.

The study will be conducted in adults with LGMD2I who have the ability to walk and rise from a chair.

Travel funds are provided by the LGMD2I Research Fund and the Samantha J. Brazzo Foundation. Those interested in participation in the study should contact the Center for Genetic Muscle Disorders at Kennedy Krieger Institute: 00+1+443-923-9525.

## International collaboration and trial readiness

### ENMC workshop on clinical trial readiness for FKRPs related muscular dystrophies

The European Neuromuscular Centre (ENMC) is an international organisation that supports research for neuromuscular conditions and aims to facilitate communication among scientists and clinicians working in the field. It is funded by a group of patient and healthcare associations and pharmaceutical industries from around Europe. The ENMC funds and organises workshops to encourage collaborative research with the aim of improving diagnosis and prognosis, finding effective treatments and optimising standards of care to improve the quality of life for affected people and their families.

In January this year an ENMC workshop looking at clinical trial readiness for FKRPs related muscular dystrophies took place in Naarden, the Netherlands. A multidisciplinary group of 20 people from 8 countries (UK, USA, Germany, France, Netherlands, Turkey, Canada and Denmark) attended the workshop, including 17 clinical and basic science researchers, a patient, a patient's parent, a representative from the Cure CMD foundation and a representative of the LGMD2i Research Fund.

The discussions at the workshop were divided in 4 sessions, looking at the following topics: clinical presentation and natural history of FKRPs deficiencies; patient landscape and registries; FKRPs function, models and therapies; and biomarkers and outcome measures.

A presentation on the Global FKRPs Registry was given during this workshop and throughout the workshop the importance of the registry as a tool to resolve the fragmentation of patient data was repeated and underlined. Nynke Koelma, a patient who attended the meeting, noted that the Global FKRPs Registry is an important tool for clinical trial readiness: <http://enmc.org/patient-participation/patient-participation/>

The workshop outcomes will be disseminated to other researchers and clinicians working in the field through a full publication in the journal of Neuromuscular Disorder. A lay report was produced following the workshops to inform patients and their families about what has been achieved at the workshop. The full lay report on this workshop can be found on the ENMC website:

❖ [Link to the ENMC lay report](#)

### Limb girdle muscular dystrophies – international collaborations for research

Another review article: 'Limb girdle muscular dystrophies – international collaborations for research' published recently in *Nature Review Neurology* provides an overview of various LGMD subtypes and shows how various international collaborations aim to increase knowledge of LGMD genetics. New DNA sequencing technologies are continuing to expand the understanding of LGMD genetics and increase numbers of diagnoses patients.

As a result a number of the international collaborations have been set up to complement current translational research (research from basic science to drug development) activities in LGMDs. The article mentions a few of such collaborations, including Neuromics, MYO-SEQ and RD-Connect – the projects were presented to you in the previous registry newsletters (Issues [4](#) and [5](#))

The review article also specifically mentions the Global FKRPs Registry and underlines its role in translational research not only as a tool for recruitment for clinical trials but also as a resource that could increase the understanding of the natural disease course.

❖ [Link to the academic journal](#)

## International collaboration and trial readiness

### Where do we stand in trial readiness for autosomal recessive limb girdle muscular dystrophies?

The recent publication in the *Journal Neuromuscular Disorders*: 'Where do we stand in trial readiness for autosomal recessive limb girdle muscular dystrophies?' reviews the progress and challenges of the translational research (research that aims at progressing the basic science to drug development) for Limb girdle muscular dystrophies type 2 (LGMD2s).

Limb girdle muscular dystrophies type 2 (LGMD2) are a group of genetically varied rare diseases that are generally characterised by progressive weakness of the shoulder and pelvic girdle muscle. Individually different types of LGMD2 are very rare, however, together they form of a significant group of conditions among other neuromuscular diseases. Over 20 disease causing genes have been identified over the last couple of decades.

The article outlines the current status of clinical trial readiness for these rare conditions. It reviews main challenges and elements enabling translational research for LGMD2. It points to the fact that understanding of disease mechanism and its course is essential to identify therapeutic strategies. It highlights that animal models are invaluable tools but need to be carefully selected. The importance of identifying appropriate outcome measures is underlined too. Examples of the recruitment of LGMD2B and LGMD2I patients into ongoing natural history studies show that people affected by LGMDs are generally keen to participate in clinical trials. The role and importance of patient registries is presented in this article too. The review also highlights that patient organisations play a central role in promoting translational research.

❖ [Link to the academic journal](#)

### 2nd ENMC workshop on dystroglycan and the dystroglycanopathies

Between 27 -29 May an ENMC workshop brought together researchers working on the clinical and basic aspects of the modification of dystroglycan. This was the second workshop looking at dystroglycan and the dystroglycanopathies. The first one took place in November 2011 and you can read what was discussed then at the [ENMC website](#).

There were 18 participants at the meeting including: clinical and basic scientists from seven different countries (France, Germany, Mexico, Sweden, The Netherlands, UK and USA) including a patient and carer and a representative from a patient organisation. The workshop reviewed a broad range of topics relevant to the dystroglycanopathies, from patient registries and clinical diagnostic approaches to the functional role of dystroglycan in muscle and brain, as well as potential new therapeutic approaches to treat the dystroglycanopathies.

There was a presentation from a person affected by LGMD2I, supported by insights from his carer. The mother of a boy with LGMD2I, and representative of the organisation Cure CMD, also gave her perspective. During the meeting Global FKRP registry was presented as well.

During the meeting a consensus was reached for the naming of dystroglycanopathies and this recommendation will be taken forward to a forthcoming ENMC workshop that will specifically address naming and nomenclature of LGMD which also encompasses several dystroglycanopathies.

A lay report was produced after the meeting and it can be found on the ENMC workshop website:

❖ [Link to the ENMC lay report](#)



## Upcoming meetings and events

### **New Directions in Biology and Disease of Skeletal Muscle Conference, 29 June -2 July, Florida, USA**

The seventh New Directions in Biology and Disease of Skeletal Muscle Conference will be held between 29 June and 2 July, in Orlando, Florida, USA. The conference brings together scientists working to understand mechanisms and develop new therapies for muscle disease, especially the muscular dystrophies. It will highlight current developments in muscle biology, disease, and therapy with presentations by leading international researchers. The conference focuses on bringing together industry and academic attendees with the aim of evaluating laboratory based observations and assessing or testing suitability for therapy in the preclinical and clinical setting.

### **The Dystroglycanopathies: 2016 Patient and Family Conference, 6 August 2016, Iowa City, USA**

The Iowa Wellstone Center presents: The Dystroglycanopathies: 2015 Patient and Family Conference. The event will feature talks from physicians and researchers, Q&A, laboratory tours, networking, and social gathering. Appointments for study exams will be available Thursday 4, Friday 5, and Sunday 7 August. Registration forms and event information and will be available soon.

### **International Congress on Neuromuscular Diseases (ICNMD) 5-9 July 2016, Toronto, Canada**

14<sup>th</sup> International Congress on Neuromuscular Diseases to be held in Toronto, Canada between 5 -9 July 2016. At the previous meeting, which took place in Nice in 2014, it was decided that the Congress would move to a two-year cycle instead of meeting every four years.

The Congress will include among others the sessions on muscular dystrophies, other myopathies, myasthenia gravis, polyneuropathies, spinal cord disorders, genetics, ultrasound and neurofibromatosis. Updates on the understanding of the genetics, pathogenesis, evaluation and treatment of neuromuscular disorders will be presented during the conference as well.

### **LGMD Awareness Day – 30 September 2016, worldwide**

The second annual Global “Limb Girdle Muscular Dystrophy Awareness Day” will be held on September 30th 2016. The goal is to globally draw attention to this group of rare neuro-muscular diseases which can impact the lives of many from childhood through adulthood as LGMD occurs in all parts of the world and among all ethnic groups. Further details about this can be found here: <http://lgmd-info.org/lgmd-awareness-day/>

### **World Muscle Society Congress - 4-8 October 2016, Granada, Spain**

The Congress will be held in the traditional WMS format with three selected topics. One day of the symposium will be dedicated to each of the selected topics addressing emerging discoveries in the field: structural myopathies and diseases of the sarcomere, adult onset myopathies: hereditary and acquired, advances in the treatment of neuromuscular disorders.

If there are any specific topics that you would like to see included in the next newsletter, please get in touch. You can contact the Registry Coordinator on the following email address: [coordinator@fkrp-registry.org](mailto:coordinator@fkrp-registry.org)

If you have any other questions you can also get in touch with your national contact from the list available on the website: [National Contacts](#)

### **REMEMBER TO UPDATE YOUR INFORMATION ON THE REGISTRY**

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