

Global FKRП Patient Registry Newsletter

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

Issue 1
April 2012



Welcome!

Dear FKRП registrant and clinician,
This is the first newsletter for patients registered with the Global FKRП Patient Registry.

In this issue you will find:

1. A brief summary of Registry goals (Page 1)
2. Your role in making the registry effective (Page 1)
3. Introduction to the Registry Steering Committee (Page 2)
4. Introduction to active patient organisations supporting the spectrum of FKRП conditions (Page 2)
5. Global FKRП Registry Statistics (Page 2)
6. FKRП Research Update (Page 3)
7. FKRП Clinical Studies (Page 4)

1. REGISTRY GOAL

The Registry goal is to identify suitable patients for future clinical trials, allowing them to be contacted quickly and giving them the opportunity to participate. Information collected in the registry can also be used to inform

researchers and clinicians about the frequency of the condition in certain countries and centres. Patients that are registered in the Global FKRП Patient Registry will be informed directly about any upcoming clinical trials or studies where they match the inclusion criteria and there would be the possibility of participation.

2. YOUR ROLE IN MAKING THE FKRП REGISTRY EFFECTIVE

Keeping your profile up to date is critical to the Registry's success. Any database is only as good as the information contained within. You will need the password you used to register. If you have forgotten this then you can be given a new one (https://www.fkrp-registry.org/registry/login/lost_password.en.html). If you notice that your doctor has not completed your doctor's form then please feel free to contact him/her directly and ask him/her to do this as soon as possible. The data needs to be updated once a year.

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

uk@fkrp-registry.org

National representatives email addresses:

australia@fkrp-registry.org
belgium@fkrp-registry.org
canada@fkrp-registry.org
catalan@fkrp-registry.org
croatia@fkrp-registry.org
denmark@fkrp-registry.org
germany@fkrp-registry.org
italy@fkrp-registry.org
netherlands@fkrp-registry.org
nz@fkrp-registry.org
spain@fkrp-registry.org
switzerland@fkrp-registry.org

3. REGISTRY STEERING COMMITTEE

The Global FKR Patient Registry is governed by a Steering Committee which consists of:

- Prof. Volker Straub, MD, PhD, Newcastle University, UK
- Dr. Katherine Mathews, MD, University of Iowa, USA
- Prof. John Vissing, MD, PhD, University of Copenhagen, Denmark
- Prof. Maggie Walter, MD, Ludwig-Maximilians-University, Germany
- Dr. Anne Rutkowski, MD, Cure CMD Chairman
- Dr. Claudia Mitchell, MBA, PhD, Director LGMD2I Fund

Information about each of the members can be found on the Registry website (www.fkrp-registry.org/team/steering_committee/index.en.html).

4. ACTIVE PATIENT ORGANISATIONS SUPPORTING THE SPECTRUM OF FKR CONDITIONS

The LGMD2I Research Fund (www.lgmd2ifund.org), a non-profit private foundation established in March 2011, focuses on finding treatments for Limb Girdle Muscular Dystrophy 2I and other related muscle diseases. Through its grants awards programme, the LGMD2I Research Fund seeks to foster basic research in the field, to promote clinical trial readiness and to support translation of promising scientific discoveries into treatments and patient care. Visit the LGMD2I Research Fund website for more information on its newly awarded grants or on resources for patients and the scientific community.

Cure Congenital Muscular Dystrophy (Cure CMD), a non-profit organisation founded in April 2008 by 3 parents, has fast-tracked a collaborative approach to finding treatments across the CMD to LGMD spectrum. Building a network of dedicated clinicians, scientists and families together with TREAT-NMD, launching a BioBank to support research, developing consensus guidelines and evaluating research and clinical trial priorities with collaborators, such as the LGMD2I Fund, Samantha J Brazzo Foundation and others, continues to build momentum. Family directed donor funding has contributed to \$800,000 funded in research and scientific conferences in the last 3 years, including the Myomatrix Scientific Conference that was led by Cure CMD and Dr. Dean Burkin, and co-sponsored by the MDA, Avi

BioPharma, PTC therapeutics, LGMD2I Research Fund, Ultragenyx, Santhera, Genzyme, Cellular Dynamics Inc and Cure CMD. A top priority for Cure CMD's Chairman whose daughter has LGMD2K, an alpha dystroglycan related dystrophy, is evaluating objectively whether steroids deliver a treatment. To review research funded by Cure CMD: <http://curecmd.org/scientists/grants>.

5. FKR REGISTRY STATISTICS

The Registry currently holds 187 patients from 19 countries around the world which is fantastic progress for the Registry's first year! We would like to say a big thank you to all of the people who are participating in the Registry and also to the clinicians from around the world who have contributed. The Registry only functions because of this collaboration.

We hope that the Registry can continue on this path and expand into other countries in the coming years extending coverage to patients in those countries that are either under-represented or not represented at all within the Registry at present.

Countries currently represented within the Registry include: United Arab Emirates, Austria, Australia, Canada, China, Czech Republic, Germany, Denmark, Spain, France, United Kingdom, India, Iran, Lithuania, Mexico, The Netherlands, Russia, Sweden, USA. (See Figure 1).

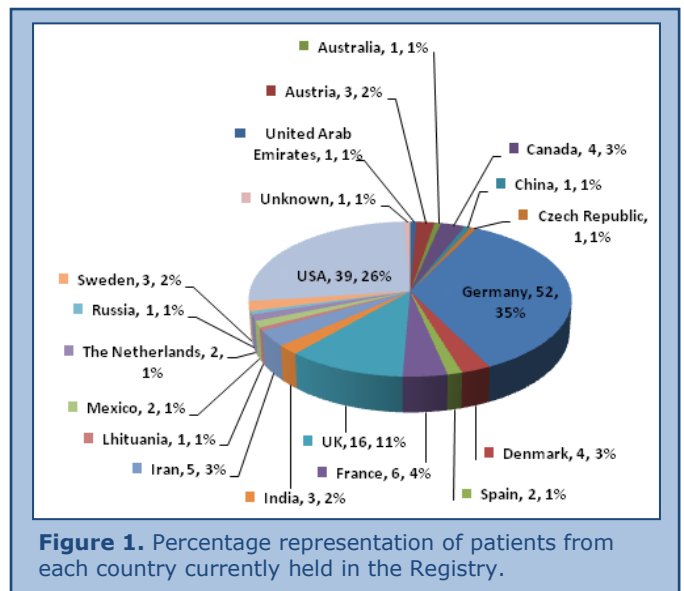


Figure 1. Percentage representation of patients from each country currently held in the Registry.

6. FKRP RESEARCH UPDATES

FKRP and Alpha Dystroglycan Related Dystrophy (αDG-RD) Research

FKRP is one of the currently 10 known genes (FKRP, fukutin, LARGE, POMT1, POMT2, POMGnT1, DPM1, DPM2, DPM3, αDG) that can lead to an alpha dystroglycan related dystrophy (αDG-RD, dystroglycanopathy). Research in this field focuses on both FKRP specifically and on the group of disorders subsumed under αDG-RD. Here are 3 currently funded research projects that may provide future insight into both FKRP and αDG-RD, what causes the muscle weakness and potential therapies.

Development of Mouse Models of FKRP

Dr. Sue Brown at the Royal Veterinary College, UK, developed 2 models of FKRP, one with embryonic brain involvement and the other with rescue of the brain phenotype, leading to a mouse model with predominantly skeletal muscle involvement. This mouse model, known as the FKRPMD, is currently being further characterised.

Furthermore, scientists at the McColl-Lockwood Laboratory for Muscular Dystrophy Research, Carolinas Medical Center, North Carolina, USA, have created several mouse models of muscular dystrophy with mutations in the fukutin-related protein (FKRP). Mutations of the FKRP gene causes diseases ranging from mild to late onset limb-girdle muscular dystrophy type 2I (LGMD2I) to earlier onset, more severe congenital muscular dystrophy (CMD) including Walker-Warburg syndrome and muscle-eye-brain disease with brain and eye defects. McColl-Lockwood Laboratory has generated several mouse models with different mutations in the FKRP gene, leading to mice with different degrees of brain, skeletal muscle and heart involvement. Two of the mouse models, one due to a P448L mutation and one modeling the common L276I mutation, may provide a valuable resource to ongoing understanding of the FKRP disorder. Ongoing efforts to characterize these animal models will define their value in preclinical drug testing.

Zebrafish, A Different Kind of Disease Model

Dr. Jim Dowling, MD, PhD, from the University of Michigan has recently been funded to generate an FKRP zebrafish model and compare this model to two different existing αDG-RD zebrafish models (POMT2, POMGnT1). This work builds upon an established program to characterise congenital muscle disease zebrafish models and allows for a comparative analysis of both zebrafish pathology and response to a medium scale drug screen across multiple neuromuscular conditions.

Targeting LARGE

LARGE is the name of one of the αDG-RD genes. Early work from Dr. Kevin Campbell's lab, University of Iowa, has shown that upregulation of LARGE (increasing the expression of LARGE) in patient derived skin cells can restore critical binding of alpha dystroglycan (αDG) to laminin 211, a function that is partially lost in people with an αDG-RD, including FKRP (Barresi *et al*, Nature Medicine (2004) 10: 696-703). Further work by Dr. Kanagawa, showed that injecting a viral vector containing LARGE into the Fukutin mouse model also improved glycosylation measured by an antibody called 2H6, which correlates with binding of αDG to laminin 211. (Kanagawa *et al*, Hum. Mol. Genetic. (2009)18(4): 621-631). Several laboratories are currently working on drug screens to identify potential compounds that might upregulate LARGE.

7. FKRП Clinical Studies

LGMD2I Natural History Study

Dr. Tracey Willis from Newcastle University (UK), who also helped to set up the Global FKRП Patient Registry, recently finished her dissertation on a natural history study of 38 patients with LGMD2I. Her project was a collaborative project between four neuromuscular centres in Copenhagen, London, Newcastle and Paris.

One of the main objectives of the study was to contribute to the "trial readiness" of LGMD2I patients. This means that the knowledge of how patients with LGMD2I perform on standardised physical testing and the relevance of the tests for this group of patients, contributes to the further preparation of designing a good clinical trial.

Whilst the physical and functional tests were subjective, magnetic resonance imaging (MRI) of the pelvic and leg muscles was also carried out to obtain an objective measure of muscle damage (pathology).

All patients were followed for one year and during this time had two MRI scans. The study represented the largest cohort to date of patients with LGMD2I studied longitudinally (over a period of time) with functional, physical and imaging assessments.

The project was funded through the MRC Centre for Neuromuscular Diseases (<http://www.cnmd.ac.uk/>), the Muscular Dystrophy Campaign, UK, the Sara and Ludvig Elsass Foundation, Denmark and the Association Française contre les Myopathies, France.

Proposed Steroid Trial in LGMD2I Patients

Discussions are underway about a potential steroid trial in patients with LGMD2I, which would be the first interventional trial for this population. The rationale behind the proposed trial is to test whether the steroid Prednisone (alternatively known as Prednisolone) will show an improvement in motor function (muscle strength) in patients with LGMD2I over a designated time period. There will be other inclusion criteria that patients will need to meet before being considered eligible to participate. The side effects of Prednisone are now well established. *Deflazacort, another steroid that is frequently used in patients with Duchenne muscular dystrophy, will not be used as it is not widely available in some countries.*

The trial will be multi-centred due to the small patient numbers and the Global FKRП Registry will be utilised to find potentially eligible patients.

The details of the trial are still to be refined and submitted to an ethics board for review and approval so this by no means guarantees that the trial will definitely go ahead. You will be informed of any updates through the registry so please ensure that your contact details are always kept up to date.

If you would like to see any specific topics included in the next newsletter then please contact:

uk@fkrp-registry.org