Issue 7
October
2018

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 7th Global FKRP Registry Newsletter!

What's inside?

Welcome to the Global FKRP Patient Registry! We are a registry (database) that collects information from individuals carrying a mutation in their Fukutin-Related Protein (FKRP) gene, regardless of disease diagnosis. Registrations are welcomed from all over the world and are voluntarily initiated online by the patient or their parent or legal guardian. The registry exists to:

Data provided by a patient and their nominated doctor is treated confidentially and with respect. Only information with personally-identifiable data removed is shared outside the registry and only with the approval of the Registry Steering Committee. The FKRP Registry is led by Professor Volker Straub at Newcastle University, United Kingdom, and may be found at https://www.fkrp-registry.org/.

Global FKRP Registry Statistics

The registry currently has 622 participants from 38 countries (**Figure 1**), with the greatest number of registrations from the USA (27.8%), Germany (21.2%) and the UK (11.7%). Though the most common founder *FKRP* gene mutation is believed to originate from the Scandinavian Region, low participant numbers from these countries suggest that they may still be under-represented. However, Scandinavian registrations are slowly increasing, for example, there have been 27 new registrations from Norway from 2017 to the present.

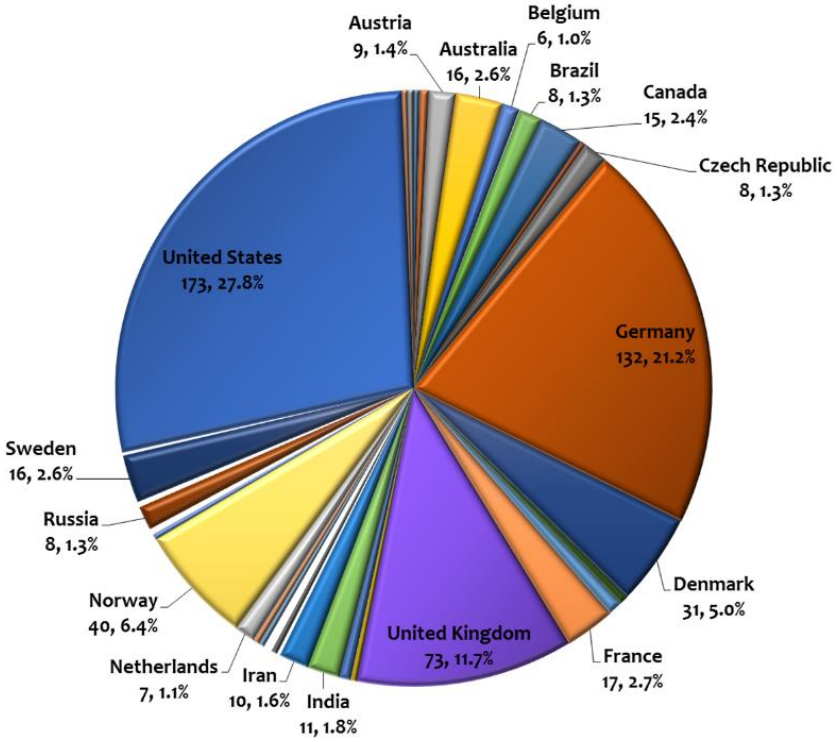


Figure 1. Pie chart showing the percentage of registered patients from each country.

United Arab Emirates	Argentina	Austria	Australia	Belgium	Brazil	Canada
Switzerland	Czech Republic	Germany	Denmark	Spain	Finland	France
United Kingdom	Hungary	Ireland	India	Iran	Iceland	Italy
Kuwait	Lithuania	Luxembourg	Libya	Mexico	Netherlands	Norway
New Zealand	Pakistan	Quatar	Russia	Saudi Arabia	South Korea	Sweden
Syria	United States	South Africa	Blank			

The year on year registry recruitment numbers are presented in **Figure 2**. Variations may occur from numbers reported in previous newsletters due to some participants registering and subsequently discovering that their condition is not FKRP-related and therefore, with their permission, their registration is removed.

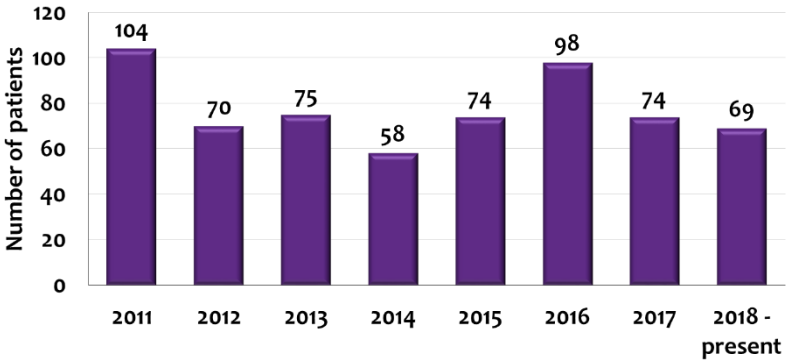


Figure 2. Number of patients that have registered per year.

The age of registry participants ranges from 0 through to 79 years, with a median age range of males between 30 and 39 and that of females, between 20 and 29 years (**Figure 3**). The median age of all participants is 36 years old.

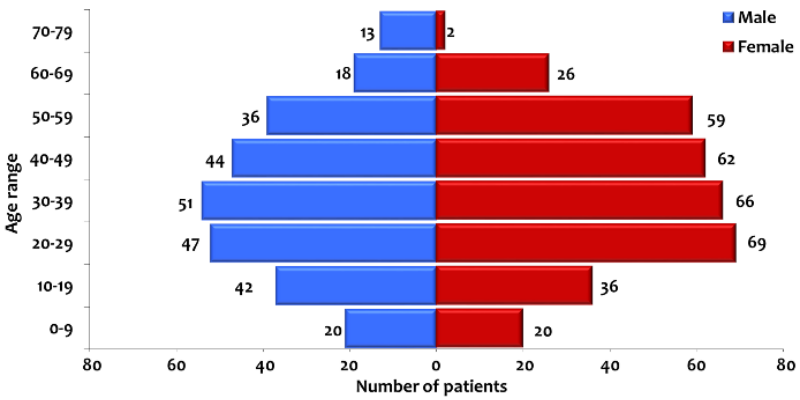


Figure 3. Age range of registered patients for males and females.

The most commonly reported diagnosis by registry participants is Limb Girdle Muscular Dystrophy 2I (LGMD2I) (86.2%, **Figure 4**). Congenital muscular dystrophy type 1C (MDC1C) was reported by 1.9% and other FKRP-related muscular dystrophies, by 2.3% of participants.

The diagnosis of quite a high number of participants is unknown - the registry is contacting these individuals to clarify their diagnosis.

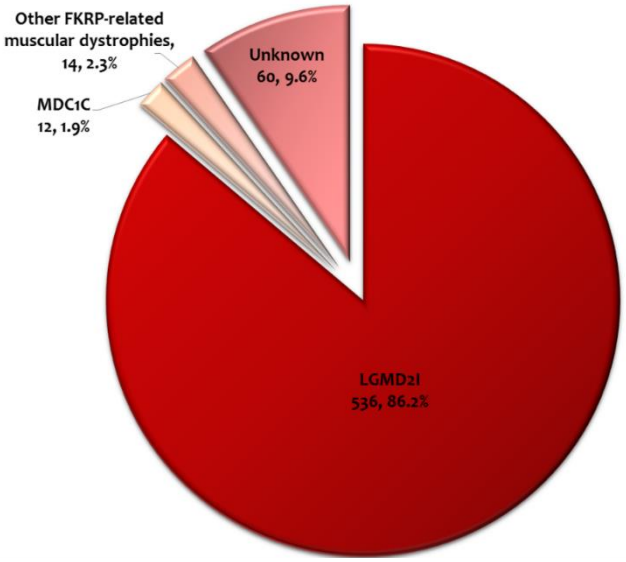


Figure 4. Pie chart showing the representation of each diagnosis as reported by **all patients**.

Genetically-confirmed patients

Globally, individuals that carry an *FKRP* gene mutation are very uncommon and one of the most important roles of the Global FKRP Registry is to make it easier to find and invite these individuals to participate in clinical trials and research studies, when they occur. To enable an individual's inclusion in such studies, it is essential that the registry knows their specific mutation. Currently, the registry has received the genetic diagnosis confirming an FKRP-related muscular dystrophy (MD) from 291 registrations. It is vitally important that we increase this number, therefore, the registry is contacting participants to request details of their genetic diagnosis.

Of the 291 patients with confirmed FKRP-related MD, 163 are female and 128 are male, and they are representatives of 23 different countries. 96.9% of these patients have LGMD2I, 0.3% have MDC1C and 1.7% have other FKRP-related MD (**Figure 5**). Again, a small percentage of participants have not reported their FKRP-related condition and the registry is in the process of seeking further information.

Among individuals with a confirmed FKRP diagnosis, the range in patient age is from 0 through to 79. In both males and females, the number of individuals in each age range is relatively evenly distributed, approximately between the ages of 10 and 59 (**Figure 6**).

When you visit a doctor feeling unwell, they review your symptoms and perform tests to reach a **medical diagnosis**. Among the muscular dystrophies, symptoms may be very similar, therefore, to be certain of the cause of your illness, it is important to have a genetic test. This will identify if a change or mutation in a specific gene is present and will provide a **genetic diagnosis** of your condition. For confirmation of your illness, certainty that you receive disease-appropriate care and inclusion in suitable clinical trials it is vital to have a genetic diagnosis.

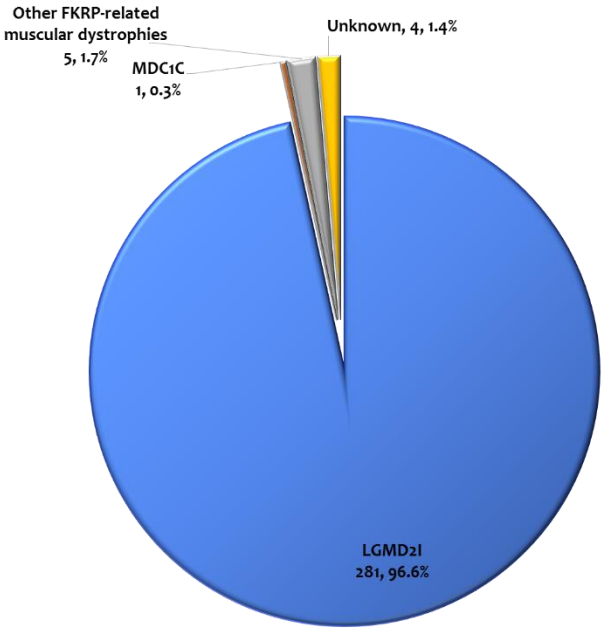


Figure 5. Pie chart showing the representation of each diagnosis as reported by **genetically confirmed patients**.

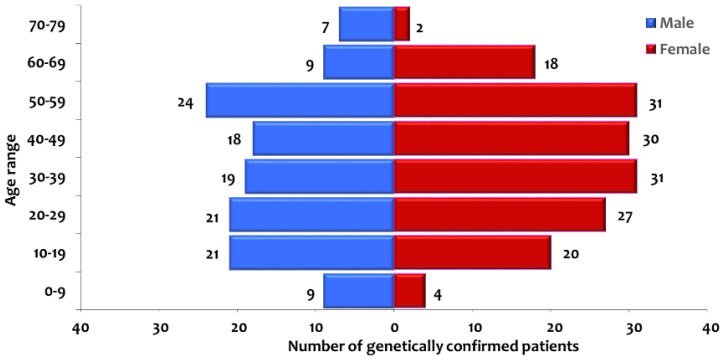


Figure 6. Age range of registered patients for males and females, for all **genetically confirmed patients**.

Family history is an important consideration when studying genetic conditions. One of the questions asked of participants is whether they know of any members of their family affected by an FKRP-related MD. Of those with a genetic diagnosis, approximately one quarter of participants said that they had an affected relative (26.2% males, 28.2% females), approximately two-thirds said that they did not and a small number of participants did not know (**Figure 7**).

A broad summary of the genetic data held in the registry is presented in **Figure 8**. We all possess two copies of the *FKRP* gene. When a change or mutation occurs within the gene, it can occur either in one or in both of these copies. When the same change occurs in both copies of the gene, it is described as a homozygous mutation and if the change is in one copy only, it is described as heterozygous. The term compound heterozygous describes when more than one heterozygous mutation is present, with at least one mutation per copy of the gene. The common mutation referred to in **Figure 8** is the founder *FKRP* mutation believed to originate from Scandinavia. Within the registry and among individuals with a confirmed FKRP-related diagnosis, the common mutation is present in a very high percentage. The homozygous common mutation is present in approximately two-thirds of all genetically-confirmed individuals.

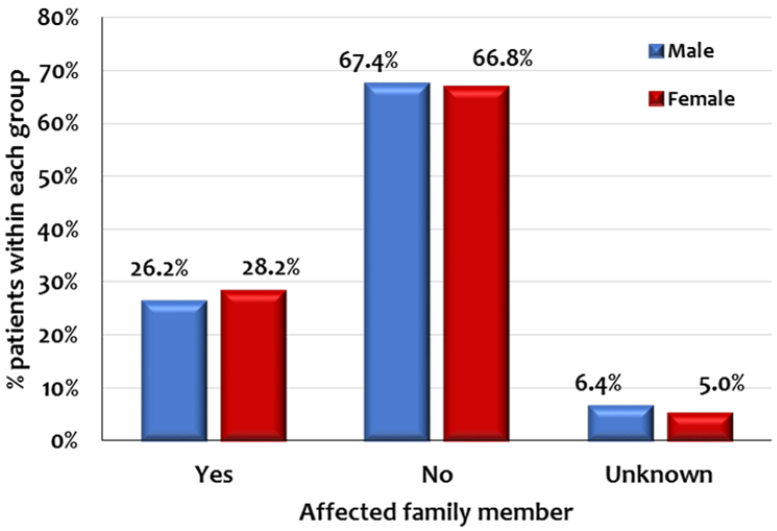


Figure 7. The percentage of individuals with affected family members among all **genetically confirmed patients,** presented in both males and females.

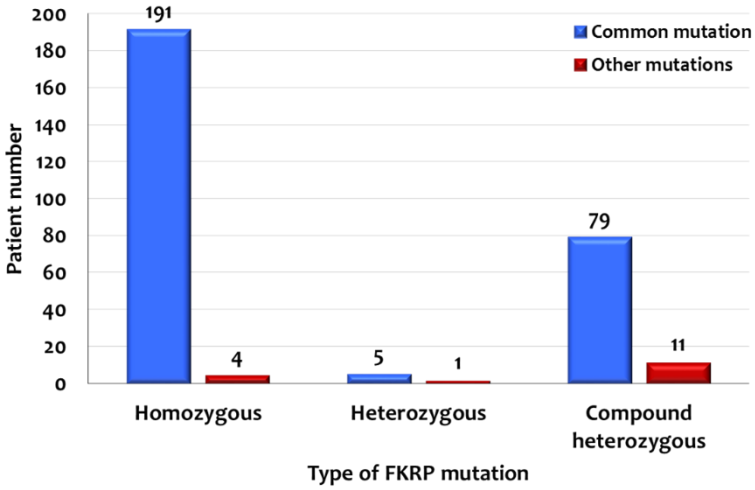


Figure 8. Number of patients affected by different mutations of the *FKRP* gene.

The FDA embraces the value of 'Real World' Data from Patient Registries in Clinical Trials

The opinions and needs of rare disease patients are increasingly shaping the design of clinical trials for new therapies. A recent article in Muscular Dystrophy News Today describes how Commissioner Scott Gottlieb of the U.S. Food and Drug Administration (FDA) is encouraging a move away from traditional, randomized clinical trials with placebo-controls, towards an approach influenced by meaningful end-points and 'real-world' data, as well as natural disease histories. In rare diseases, the FDA is increasingly engaging with patient advocacy groups and recognizing the value of the data held in Patient Registries, which gather data on very small patient populations, frequently including disease natural history and progression.

The full article may be found at https://musculardystrophynews.com/2018/03/12/rare-disease-groups-welcome-fdas-embrace-real-world-data-clinical-trials/.

Remember; our Registry is only as useful as the data within it, so please make sure you keep your information up to date, and contact us if you have any questions or problems.

Steering Committee Update

In March 2018, Professor Laurence Bindoff, of the University of Bergen and Haukeland University Hospital, Norway, stepped down from the Global FKRP Patient Registry Steering Committee. We would like to thank Laurence for his invaluable contribution to the Registry over the years and we wish him well for the future.

Dr Synnøve Jensen, coordinator of the Norwegian Registry of Hereditary and Congenital Neuromuscular Diseases, has kindly agreed to join the Steering Committee in Professor Bindoff's place. Synnøve is a consultant neurologist, partly affiliated with the Neuromuscular Center (NMK) at University Hospital of North-Norway (UNN) in Tromsø. Synnøve joins the existing seven members of the Global FKRP Steering Committee.

Patient's Stories

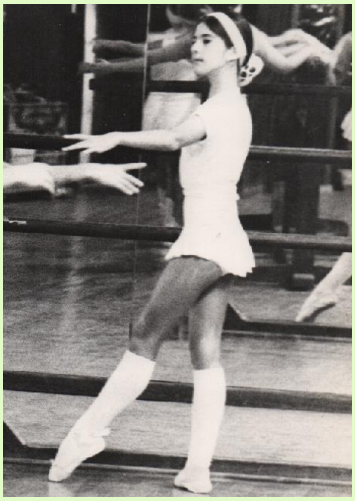
We would like to share with you patients' stories through the registry website and the newsletter. Please get in touch with us if you would like to share your story with us.

'The Story of my Life' — Marta Quezada, Mexico

I consider myself a very lucky person. I was born in a close and loving family that has helped me all my life.

When I was born I was a chubby baby, my nickname was 'Gordita'. Soon I grew up and became a very slender girl who wanted to become a ballerina. At five years old, I entered the Royal Academy of Dancing. I continued taking lessons until I was about 13 years. I stopped because I could not jump high and could not raise my legs.

Disappointed, I decided I was going to do another type of dancing and I continued doing modern dance until I was 16.



I loved to dance but sports were a torture. I still did not know I had a medical problem so I was a victim of bullying and scolding by my gym teacher. In 1978 after a bad episode in my gym class, where I ended crying and with a lot of pain, I went to an orthopaedist because I got tired very fast and my legs hurt. At that time, there were no doctors in Mexico that could diagnose MD so he suggested to travel to the United States…

Read the full story on the registry website.

'My new life with Limb Girdle' — Roar Orekåsa, Norway

I am a man of 57 years old, married and father to three adult children. I worked as a director of a large international company, in charge of three companies. Following many examinations, I was finally diagnosed with LGMD2I approximately two years ago.

For several years, I wondered why I could not get stronger or in better shape given all my training and the active life that I and my family lived; snowboarding and skiing in winter, hunting and hiking in the summer and two to three sessions per week in the gym. I felt I was only getting weaker each year. I have always been an active person with many balls in the air both at work and in private. I worked for many years in defence as a rescuer on the Sea King rescue helicopters, a job that requires you to stay in good shape. I noticed something was wrong in my late thirties but it was another 15 to 20 years before I consulted a doctor to further investigate. I had never heard of Limb Girdle before I received the diagnosis. It was a shock to receive but also, a bit of a relief. Finally, I had an answer as to why I could not run anymore, had trouble climbing stairs and getting up from a chair etc. I stopped snowboarding and skiing three years ago but I continue to visit the gym…

Read the full story on the registry website.

Research Updates

A therapy for the treatment of disease develops from an idea, founded on scientific observations. This theory is initially explored in the laboratory, in the Petri dish (*in-vitro*), to investigate the effect of a potential therapy in a simplified system, outside of the body. If this step suggests an encouraging result, the effect of the therapy is then evaluated in an animal model to observe the effect on an organism as a whole. Only following the successful conclusion of these pre-clinical studies may the potential therapy be considered for clinical trial in humans. Animal models of disease are a useful tool to investigate both how a therapy is tolerated and its impact on the disease itself. To this end, models of FKRP-related disease have been generated in mice.

Natural history

Natural history studies collect health information over time to further our understanding of how a disease develops and to give insight into how it might be treated.

Such a study was performed by a group in Iowa City, USA, who investigated the association between childhood activity and sport participation and the severity of LGMD2I in later life. In a group of forty-one patients, they were able to find no relationship between self-reported childhood activity levels and disease course later in life. The group concluded that childhood activity does not negatively impact on severity of LGMD2I.

Link to the scientific article: Brun *et al* (February 2017).

Mouse models…

In the previous registry newsletter, development of the mouse models carrying the common L276I mutation was described. More recently, a number of groups have published their research characterizing mouse models carrying the *FKRP* mutation P448L. They studied the general health, progression of disease, changes in physiology and biochemistry and changes in muscle structure and function of these mice to understand their natural history and to evaluate whether they are representative of disease development in humans. Their collective research recognises several markers of disease pathology that are shared between P448L mice and human subjects with LGMD2I, concluding that they are a valuable model of LGMD2I.

Links to the scientific articles: Blaeser *et al* (October 2016); Maricelli *et al* (June 2017); Yu *et al* (April 2018).

…and their use…

A group in North Carolina, USA, used mice of the mutant *FKRP* model P448L to investigate the effect of tamoxifen and raloxifene. These drugs are used in the treatment of a number of human conditions and have anti-inflammatory, anti-fibrotic, bone-protective and muscle building effects, all of which would be desirable in a therapy for LGMD2I. The researchers dosed the mice daily for one year and monitored muscle strength and endurance, cardiac and pulmonary functions and levels of fibrosis and muscle deterioration. They observed that the drugs significantly slowed disease progression. However, tamoxifen caused severe adverse effects on male reproductive organs. Their results suggest the exciting potential of these drugs in FKRP-related muscular dystrophy therapy though careful consideration of drug and dosage selection in males and in females is required.

Link to the scientific article: Wu *et al* (April 2018).

Gene therapy

Gene replacement therapy is currently being developed for the treatment or prevention of disease in patients who carry specific genetic mutations. The therapy involves the delivery of a healthy copy of the mutated gene into the cells in a patient's body that need it most. This healthy gene is tailored to respond to molecular signals within particular cell types, so that the gene's protein product is preferentially made in desired cell types, for example, muscle cells.

In 2017, research was published demonstrating the positive effects of *FKRP* gene replacement therapy in mouse models of FKRP-related disease. A group in North Carolina, USA, delivered a copy of the healthy human *FKRP* gene to the cells of the P448L mutant mouse model using a viral vector (AAV9), a small, modified virus which is unable to self-replicate, lacks pathogenicity and is able to persist stably in muscle tissue. They administered this treatment in a single dose to mice in various stages of disease progression. The protein encoded by the *FKRP* gene modifies the structural protein α-dystroglycan (α-DG). Mutations in the *FKRP* gene impair this activity leading to a reduction or loss of function of α-DG. Following treatment, the team observed restored modification of α-DG, restored muscle function and improvement in muscle structure at all disease stages. However, mice in the later stages of disease showed less improvement.

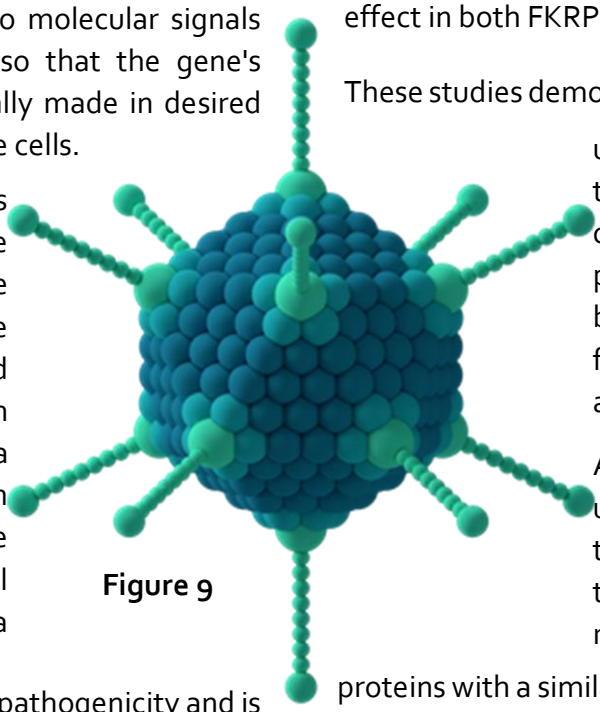


Figure 9

A similar study was carried out by scientists at Généthon, France. They used a mouse possessing the most common *FKRP* mutation, L276I. In these mice, the FKRP protein was expressed as normal but its function was impaired, leading to the development of moderate muscular wasting and weakness from six months of age. A similar modified virus to that previously described was used to deliver a single dose of the healthy *FKRP* gene to the mouse cells. At a low dose, improvement in protein function and muscle function and structure was observed. However, at a high dose, the group observed a detrimental effect in both FKRP- and wild-type mice.

These studies demonstrate proof of concept of the use of gene therapy in the treatment of FKRP- related conditions. They reveal the potential for future therapies but also the need to further fine-tune the system before its application in clinical trials.

An alternative approach in the use of gene replacement therapy has been explored by a team in Milan, Italy. It has recently been observed that proteins with a similar function to that of FKRP are detected in the blood. The group therefore speculated that these blood-borne proteins may be able to act remotely on tissues of the body. To this end, they introduced the healthy human *FKRP* gene, via a modified viral vector, into cells from the *FKRP* mutant mouse model L276I that were grown in the laboratory. They detected that healthy FKRP protein was made and secreted from the cells. The group then introduced these modified cells into mice of the same *FKRP* mutant line. Excitingly, the resulting healthy FKRP protein was detected in the blood of these animals. Restored modification of α-DG and an improvement in muscle strength was detected suggesting that the systemic supply of FKRP protein was able to recover function.

Links to the scientific articles:
Vannoy *et al* (March 2017); Gicquel *et al* (May 2017); Frattini *et al* (October 2017)

Figure 9. A cartoon image of an Adeno-associated virus (AAV), used as a viral vector.

The renaming of the LGMDs…

…from LGMD 2I to LGMD R9 FKRP-related

Limb Girdle Muscular Dystrophy (LGMD) 2I is the most common condition caused by mutations in the *FKRP* gene. First described in the 1950s, the LGMDs are a group of rare neuromuscular diseases that has progressively grown to be a large and diverse group of conditions. This growth presents an increasing challenge in the logical naming of successive conditions. To address this increasing complexity in classification and naming of the LGMDs, a European Neuromuscular Centre (ENMC) workshop (March 2017, at Naarden, Netherlands) was held in which clinical experts, experts for disease classifications, patients and representatives of patient organisations participated.

First proposed in 1995, the original classification of LGMD subtypes assigned a number, to indicate whether they are inherited in a dominant ('1') or recessive ('2') manner, and a unique letter, for example LGMD 2I. However, this method of naming has reached its natural limit as the condition LGMD 2Z has been identified. It is therefore an appropriate time to re-visit and update this nomenclature.

Delegates first considered the definition of LGMD. There are currently more than 30 genetic subtypes of LGMDs, many of which have little in common. Increases in understanding of the molecular and disease characteristics of the LGMD subtypes enabled the workshop to agree an updated definition of this disease group. A number of alternative naming strategies for the LGMDs were proposed and a consensus achieved on a single, new nomenclature. It was proposed that LGMDs should now be named with a letter to indicate the mode of inheritance, 'D' for dominant and 'R' for recessive; the inclusion of the affected protein associated with the condition; and a unique number based upon the order of discovery of the affected protein. It was concluded that this new system of classification followed more precise disease definitions, provided a good description of the affected protein and means of inheritance and would be robust for the addition of more conditions as they are discovered. Patients and patient organisations participated in the discussion and advised that this change be explained to patients in an accessible manner – emphasising that the proposed change is not simply an academic exercise but is a necessary step to enable more precise identification of disease type and that the previous nomenclature had reached its natural limit. Patient representatives were concerned that this change in nomenclature should not cause confusion, for example in the provision of care or disability welfare funding received, and should encourage engagement with pharmaceutical companies to invest in LGMDs.

After considered discussion, delegates of the ENMC workshop reached consensus in the proposal of the new nomenclature for the LGMDs. In this new classification, LGMD 2I is now renamed as **LGMD R9 FKRP-related**. The names of the other conditions caused by *FKRP* gene mutation, Congenital Muscular Dystrophy type 1C (MDC1C), Walker-Warburg syndrome and Muscle Eye Brain disease (MEB), remain unchanged.

Link to the scientific report: Straub *et al*

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

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

PLEASE REMEMBER TO UPDATE YOUR INFORMATION IN 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.