



Welcome to the seventh GNE Myopathy Disease Monitoring Programme (GNEM-DMP) newsletter and thank you for your continued support and participation in the GNEM-DMP. Our newsletter is intended to provide you with regular updates on the GNEM-DMP and provide you with scientific updates related to GNE myopathy. We welcome your feedback and suggestions on this newsletter.

In this 7th Edition of the GNEM-DMP Newsletter:

- GNEM-DMP Registry Update and Participation Overview
- Use of Orthotics in Neuromuscular Diseases
- GNE Myopathy International - Overview of Activities
- Autosomal Recessive Inheritance and GNE myopathy
- 10 Tips for Family & Caregivers
- Mona Patel - My Story So Far

To join the GNE Patient Registry please visit: www.gnem-dmp.com

For more information on the GNEM-DMP contact: HIBM@treat-nmd.eu

For more information about Ultragenyx Pharmaceutical Inc. please visit: www.ultragenyx.com/patients/gnem

For more information about TREAT-NMD please visit: www.treat-nmd.eu



GNEM-DMP Registry Update and Participation Overview

Fig1: The GNEM-DMP Registry homepage at www.gnem-dmp.com



January 2017 saw the GNEM-DMP registry surpass 300 registered participants, a fantastic achievement that could only have been achievable by the amazing support and contribution of every patient, clinician, patient organisation, caregiver and other advocate of the study across the globe. Thank you for all of your support!

The registry was first made live online in March 2014 and within one year had recruited 157 participants from 21 different countries. This amazing recruitment drive was only possible due to the incredible support we received from the wider GNE community. The registry on average recruits 9 new participants per month (Fig 2) and through this continued supply of participant information, the registry is still able to guide researchers in the design of clinical trials and development of potential treatments. With the registry bringing together people with GNE myopathy; doctors, researchers and treatment developers are able to collect and share the anonymous disease information to help improve the standard of care for everyone with GNE myopathy, whilst opening doors to a greater understanding and future treatment of the disease.

Today, the registry has been active in recruiting participants for three years and the current number of members stands at 305 spanning 31 countries across 5 continents (Fig 3). The aim of the registry is to become a useful resource for participants where they are able to track their disease progression over time against other members of the registry. In order to be able to do this, the registry requires all participants to provide longitudinal data for up to 15 years (to complete questionnaires at different intervals: initially 6 months after completing their first questionnaire, then again at 12 month intervals). Every registry participant is able to log in to their online account and view all information that they have previously provided in the form of answers to the questionnaires. The registry curator notifies participants that they are due to complete a follow up questionnaire by emailing them well in advance of the questionnaire deadline – however participants are able to log in to the registry at any point to see if a questionnaire is available to them. Your primary registry contact is available at hibm@treat-nmd.eu

Tips for all Registry Participants

- Keep a Record of your username and password so that you don't have any problems accessing your registry account – but remember to keep your details secure!
- If you do have any problems accessing your account on the registry contact the curation team at hibm@treat-nmd.eu
- Ensure that emails from hibm@treat-nmd.eu or phillip.cammish@ncl.ac.uk do not direct to your spam junk folder – the curation team send numerous emails to participants about a range of GNE related topics and we wouldn't want any participant to miss out!
- Ensure that you answer as many questions in each questionnaire as you are able to – each answer provides vital information that helps power research in to GNE myopathy.
- If you are ever unsure about your participation in the registry get in touch with us!
- If you are a caregiver, friend or family member of a participant in the registry whose circumstances may have changed which affects their participation in the registry, please let us know.
- Archive of all GNEM-DMP newsletters available at: www.gnem-dmp.com/Home/Newsletters

Fig 2: Monthly Breakdown and Average of Registry Participants per Month

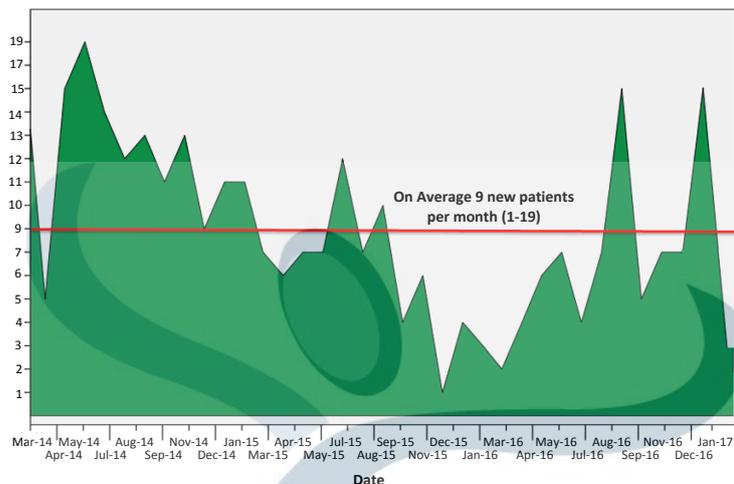
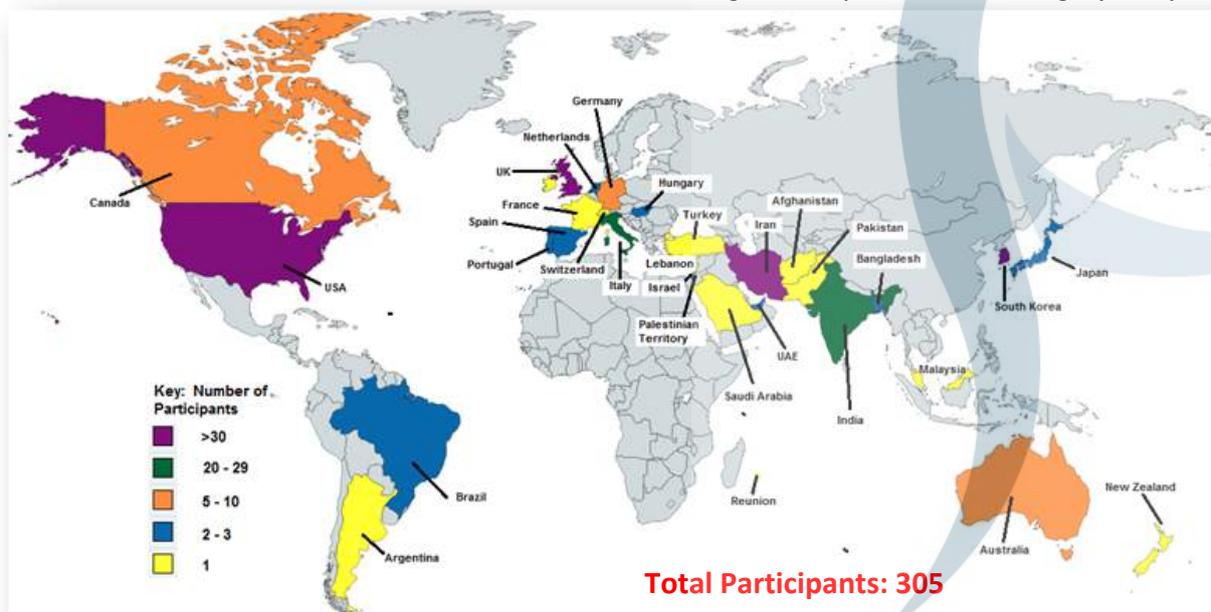


Fig 3: Global Spread of GNEM-DMP Registry Participants



Use of Orthotics in Neuromuscular Diseases -

Information from the Physio team based in Newcastle, UK.



Many people who are diagnosed with GNE myopathy will already use orthotics on a daily basis to help with their mobility, or at some point in their lives will need to use them. People visiting the clinical centre in Newcastle UK, often have a wide range of questions about the use of orthotics, which the physio team based at the John Walton Muscular Dystrophy Research Centre are able to help with. In this article Dionne Moat, who is a Neuromuscular Research Physiotherapist shares information on a wide range of topics related to orthotics specifically related to their use in patients with GNE myopathy.

What is an orthotic?

An orthotic is defined as 'an externally applied device used to modify the structural and functional characteristics of the neuromuscular and skeletal systems'⁽¹⁾. They come in a variety of shapes, sizes and materials and can be used for many different reasons for different parts of the body but primarily lower limbs.

What are they used for?

Orthotics are prescribed to maintain or improve range of movement, improve the position of a joint, to restrict unwanted movement, help manage pain, to improve function or any combination of the above. Depending on the condition, the symptoms and problems the patient is experiencing will determine which type of orthotic is recommended.

What are they commonly used for in GNE?

One of the most common initial presenting symptoms in GNE is 'foot drop'⁽²⁾. Foot drop in neuromuscular disease such as GNE is caused by weakness of the dorsi flexor muscles⁽³⁾. These are the muscles on the front of the lower leg (shin) and are responsible for pulling the ankle upwards. In some cases, or as the disease progresses, other muscles around the ankle may become weak as well causing the foot to become weak and the ankle unstable. Weakness in these muscles around the ankle also increases the risk of developing tightness in the calf muscles⁽⁴⁾. Weakness around the ankle or 'drop foot' can have a significant impact on walking, function and confidence⁽⁵⁾. Walking changes as a result of ankle weakness as an inability to pull the ankle and foot upwards during walking makes it more difficult to clear the foot and can lead to catching the foot, causing trips and falls.

Fig 1: Normal walking pattern of ankle lifting and toes clearing the floor.

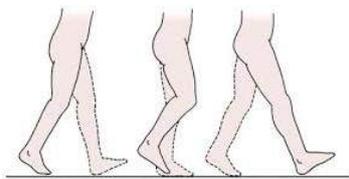


Fig 2: Pattern of walking with foot drop where ankle does not lift and toes catch the floor as leg swings through.

This in turn may lead to anxiety and loss of confidence and can mean people do less walking. This reduction in physical activity may lead to secondary weakness caused by deconditioning⁽⁵⁾. However this disuse atrophy unlike the underlying muscle weakness caused by GNE can be reversed if activity is improved. Orthotic provision is commonly used in the management of drop foot in neuromuscular disease^(4,5,6) and provision is based upon clinical expertise and reasoning by the clinician and orthotist⁽⁵⁾. The success of the orthotic is usually measured by the patients' experience of wearing it over time and also some measures of function that the clinician might record. For example, how quickly or far the patient can walk, how they move around or how they perform everyday activities using the orthotic compared to without.

The aim of using an orthotic in the management of foot drop is to provide the required level of support to the foot and ankle to maintain a good position and to ultimately improve walking and the patients ability to perform daily activities safely and efficiently. The orthotic helps to prevent catching the foot during walking reducing the risk of falls. It can also help reduce some of the aches and pains which develop as a result of people altering their walking due to the foot drop^(5,6).

Types of orthotics for foot drop

There are MANY different types of orthotic splints and what is suitable for one person, may not be suitable for the next even if they have the same condition or similar symptoms. It is advisable that a qualified professional for example a physiotherapist and or orthotist assess for and provide the correct orthotic whether this be an 'off the shelf' orthotic or a bespoke, custom made device. It is important to get the correct, well-fitting device to ensure comfort, tolerated use and to provide the most satisfactory outcome. Splints can become worn and may need to be refashioned, replaced or reassessed if needs have changed. Different localities all have different service provision and budgets and therefore the process for appointments and reviews may vary. Below are a few examples of the variety of orthotics that can be used in the management of foot drop in neuromuscular disease:

Foot Up

This is often the first device tried. It is simple to use and can be worn inside the shoe. Simple elasticated straps provide a minimum amount of "foot up". There is a plastic inlay that can fit between the laces and tongue of the shoe.



Carbon fibre AFO

These are often lighter weight than the standard rigid AFO but are not suitable for everyone as they may not provide the appropriate support around the inside and outside of the ankle.



Anterior shell AFO

These splints help with foot drop but may also assist in keeping the knee straight. As the quadriceps muscles (muscles on the front of the thigh) remain stronger in GNE myopathy, these splints are not commonly used for this condition.



Rigid AFO

These splints provide more substantial support for severe foot drop. They can be 'off the shelf' or custom made and can also sometimes have a strap at the ankle. A larger shoe is usually required to accommodate the splint.



Silicone AFO

This is a custom made splint that requires a cast of your leg to be made. It provides support around the ankle but is more flexible than rigid plastic and allows for more sensory feedback than the solid material splints. These are not readily available in local NHS orthotics departments.



Toe off

This splint helps with 'toe off' which is the moment you push off with the ball of your foot when you take a step as well as preventing foot drop.



Push aqu

This is a flexible splint that offers medium support around the foot and ankle. It has 3 elasticated straps that are wound around the ankle. They need to be pulled fairly tight to provide the appropriate support. Each strap is labelled with 1, 2, or 3 dots indicating which order the straps go in ie 1 dot = 1st strap. This splint helps to lift the foot but also provides stability around the ankle.



We recommend that you consult your health care provider or Physiotherapist before beginning to use any orthotic device. If you have any questions about any of the items discussed in this article, please contact the registry team: HIBM@treat-nmd.eu

1) Schuch, C. M., & Pritham, C. H. (1994). International Standards Organization Terminology: Application to Prosthetics and Orthotics. *JPO: Journal of Prosthetics and Orthotics*, 6(1).
2) Nishino, I., Carrillo-Carrasco, N., & Argov, Z. (2015). GNE myopathy: current update and future therapy. *Journal of Neurology, Neurosurgery, and Psychiatry*, 86(4), 385–392. <http://doi.org/10.1136/jnnp-2013-307051>
3) Sackley, C., Disler, P. B., Turner-Stokes, L., Wade, D. T., Brittle, N., & Hoppitt, T. (2009). Rehabilitation interventions for foot drop in neuromuscular disease. *The Cochrane Database of Systematic Reviews*, (3).
4) Jaivin, J. S., Bishop, J. O., Braly, W. G., & Tullos, H. S. (1992). Management of Acquired Adult Dropfoot. *Foot & Ankle International*, 13(2), 98–104.
5) Ramdharry, G. M. (2010). Rehabilitation in practice: Management of lower motor neuron weakness. *Clinical Rehabilitation*, 24(5), 387–397.
6) Ramdharry, G. M., Day, B. L., Reilly, M. M., & Marsden, J. F. (2012). Foot drop splints improve proximal as well as distal leg control during gait in Charcot-Marie-Tooth disease. *Muscle & Nerve*, 46(4), 512–9.

GMI (GNE Myopathy International) are an international group of GNE myopathy patients, family and friends with the mission to generate awareness among patients and communities worldwide about this rare genetic disorder, and to provide information and support to patients. We are located in many countries including Asia, Europe, Middle East and United States of America.



Members of the GNE Myopathy International Team

Introduction

GMI was founded in 2014 and is a consortium of GNE myopathy patients, their families and friends, drawn from all over the world. It is allied to and supported by WWGM (World Without GNE myopathy, a Trust registered in India). Our members and advocates are working actively towards increasing the awareness of GNE myopathy worldwide, and keeping abreast of latest developments in research with therapeutic potential. We are reaching out to patients and their families in our respective countries to share information, and to help newly diagnosed patients. We fervently believe collectively we will help find a cure for GNE Myopathy through advocacy, education, and research.

Patient Webinars

In keeping with our vision that the path to effective treatment is through collective patient action, we provide a platform for patients to come together and acquire information about GNE myopathy through regularly organized patient webinars which are becoming highly popular in our community, and are attended by participants from various countries including Israel, Italy, Saudi Arabia, Pakistan, India, the U.S.A, U.K. and the U.A.E.

First Patient Webinar

Title- **"GNE Myopathy Therapies: A Critical Analysis of Current Knowledge"**

Speaker: WWGM Managing Trustee, Professor Alok Bhattacharya Held on: September 17, 2016.

Various potential treatment options were discussed including gene therapy, stem cell therapy, mRNA expression, in addition to supplementation with Sialic acid/ManNAc. It was concluded that the way forward for clinical studies would be to follow those potential therapies that are in an advanced stage of development for other genetic disorders, and adapt them for GNE myopathy.

Second Patient Webinar

Title- **"Moving the Needle (ON Advances) in GNE Myopathy"**

Speaker: Lalé Welsh, CEO of the Neuromuscular Disease Foundation (NDF) Held on: December 3, 2016

Ms. Welsh discussed the current and the future state of treatments for GNE myopathy such as the ongoing clinical trials for Sialic Acid and ManNAc as well as the potential for gene therapy and stem cell therapy. She explained that the NDF are conducting Pre-Investigative New Drug (IND) work for submission to the US FDA for clinical trials for gene therapy.

Third Patient Webinar

Title: **"Stem Cell Therapy for GNE Myopathy"**

Speakers: Dr. Todd Malan, Roberta Çirışyan and Professor Alok Bhattacharya Held on January 28, 2017

More than 45 participants from various parts of the world joined this webinar discussing stem cell therapy and its applicability for GNE myopathy patients. The first presenter, Dr. Todd Malan (Innovative Cosmetic Surgery Center, Arizona, U.S.A.) talked about stem cells that are present in adipose (fat) tissues of our body. He stressed that they have studied the safety of stem cell use in general (not specific to muscle diseases) and the safety is better than previously anticipated. Further, he hypothesized that positive effect if seen in the study group (non-GNE or muscle disease), may be due to the release of a variety of growth promoting and tissue healing substances which help in repairing damaged tissues. The next presenter Prof. Alok Bhattacharya (Jawaharlal Nehru University New Delhi), gave an overview of the different types of stem cells. Ms Roberta Cirisyan, a GNE myopathy patient was the third speaker on this webinar. She discussed her stem cell treatment administered by Dr. Stavros Alevrogiannis (Athens, Greece). Ms. Cirisyan underwent stem cell transplant in 2016 and started taking various vitamins and minerals per Dr. Alevrogiannis recommendation. This is not a clinical trial but an exploratory study in one patient. The treatment continues and the conclusions are to be drawn at a later date. Following each speaker there was a question and answer session.

Flyers

The GMI team along with many dedicated volunteers have been involved in increasing awareness of GNE myopathy in the community by making and translating flyers describing GNE myopathy in many languages. These can be downloaded from our website (www.gne-myopathy.org). In addition, we have sent these flyers and contacted doctors worldwide informing them about GNE myopathy.

Patient Survey

GMI have also developed a short survey to collate patient-driven information on the effectiveness of various therapies/treatments/exercises being used. This survey was completed by more than 50 patients. The results of the survey will be available shortly.

Those who are interested to help us achieve our goals please contact GMI at: wwgm.india@gmail.com

Autosomal Recessive Inheritance and GNE myopathy



10 Tips for Family & Caregivers



Caregiver Action Network (CAN) is a non-profit organisation based in the United States of America who provide education, peer support, and resources to caregivers, working to improve the quality of life for the more than 90 million Americans who care for loved ones with chronic conditions, disabilities, disease, or the frailties of old age. They have recently published a list of tips (below) that are designed to help those in the position as a caregiver of anybody, including those who care for a person with GNE myopathy. The full article can be found on CAN's website: www.rarecaregivers.org. Please share this article with anybody you know who you feel may benefit from the information it provides.

1. Seek support from other caregivers. You are not alone!
2. Take care of your own health so that you can be strong enough to take care of your loved one.
3. Accept offers of help and suggest specific things people can do to help you.
4. Learn how to communicate effectively with doctors.
5. Caregiving is hard work so take respite breaks often.
6. Watch out for signs of depression and don't delay getting professional help when you need it.
7. Be open to new technologies that can help you care for your loved one.
8. Organise medical information so it's up to date and easy to find.
9. Make sure legal documents are in order.
10. Give yourself credit for doing the best you can in one of the toughest jobs there is!

The GNE gene is located at Chromosome 9 (exact location 9p13.3)

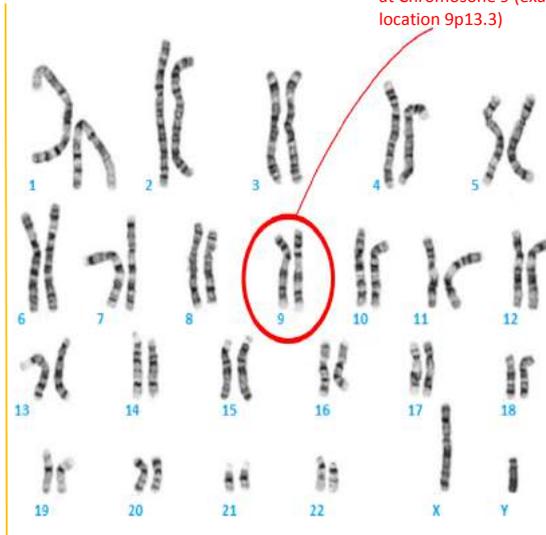
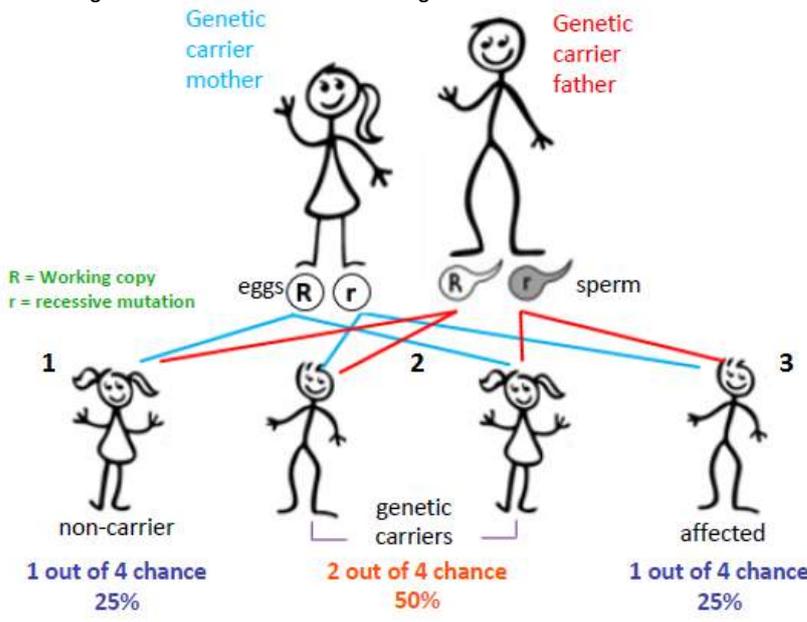


Fig 1: Chromosome picture (karyotype) showing the GNE gene

Genetics – The Basics

- Your genes contain the instructions for your body to grow, develop and remain healthy. Some changes to genes make them faulty which results in the message not being read correctly/at all by the cell.
- There are usually 46 chromosomes in each cell that are arranged into 23 pairs. One of each pair is passed on to us from our mother and the other from our father. 22 of these chromosome pairs are numbered. These numbered pairs are known as the autosomal chromosomes. The 23rd pair is made up of the sex chromosomes called X and Y. Males have an X and a Y chromosome and females have two copies of the X chromosome.
- A variation found in a faulty gene is called a mutation. If a genetic condition only occurs when both copies of the gene are changed, this is called a recessive mutation.
- An autosomal gene is a gene located on a numbered chromosome and usually affects males and females in the same way.

Fig 2: Genetic illustration demonstrating autosomal recessive inheritance.



As shown in Figure 2, where the gene containing a recessive mutation is represented by 'r' and the working copy by 'R', there are four possible combinations of the genetic information to be passed on in every pregnancy. This means that in every pregnancy there is:

1 - non-carrier. 1 chance in 4 (25% chance) that their child will inherit both copies of the working gene and will be unaffected by the condition and not a genetic carrier.



2 - genetic carriers. 2 chances in 4 (50% chance) that their child will inherit the recessive gene mutation and the working copy of the gene from the parents and he/she will be an unaffected genetic carrier of the condition, just like the parents.



3 - affected. 1 chance in 4 (25% chance) that they will have a child who inherits both copies of the recessive gene mutation from his/her parents. In this scenario, no working gene product will be produced and their child will be affected by the condition caused by this gene.



Mona Patel - My Journey So Far

Mona is from the United Kingdom, of Indian heritage and was diagnosed with GNE myopathy in 2005. Mona is a participant in the GNEM-DMP registry and has been active in fundraising campaigns with a specific focus on raising awareness of GNE myopathy. Below Mona talks about living with the condition and shares some stories about herself – please note that Mona's experiences are her own and are not representative of all study patients.



Thailand: Elephant Farm (2000)

Life before my Diagnosis

Throughout my teen years and in to my early 20s, I achieved many things of which I am extremely proud of. I have completed a 25mile (40.2km) walkathon for charity, moved away from home to attend university, climbed the Sydney Harbour Bridge and scuba dived in the Great Barrier Reef in Australia. I even gave birth to my daughter after 28hrs of labour on only gas and air!!

I was also a very keen swimmer and enjoyed participating in yoga, Pilates and dancing before my disease progressed. Just like any normal teenager or young adult, I had many hopes and aspirations for my future. I was an able-bodied person who was active and very independent until my mid-twenties and so the disease came as a shock to me and particularly to loved ones around me. I always embraced life and everything it had to offer, but I had no idea what the future held for me.

My Life at Present

Over the years since the onset of the disease, GNE myopathy has slowly deprived me of my muscle strength - to the point now where I need to depend on various equipment/mobility devices to help me with every day activities and to get around.



GNE myopathy is a progressive muscle-wasting condition that started to affect me when I was 26yrs old. I am at a stage now where a lot of my mobility is limited by the disease. I can't run, climb stairs and there's a continual feeling of vulnerability in case I fall. I can't do the things most people take for granted like popping to the shop to buy a loaf of bread, getting dressed, reaching up to get something off a shelf or to scratch the top of my head...(you catch my drift). As soon as I start adjusting to my condition, I lose another function, so have to start the process again - the challenges are endless and I find myself continually grieving the loss of another ability. What's worse is that the disease makes me feel 'needy' and I find that difficult to deal with - but I don't have a choice. The one thing I do have a choice over is how I deal with this disease.

Not letting GNE myopathy hold me back

I have created strategies to help me manage all the insensitive changes to my body. This disease has taught me about resilience and empathy. In addition, it's helped me to confront barriers and stigma in order to make a difference to the lives of other disabled people. So now, I am an award-winning Equality & Diversity Specialist working for an award-winning University, I am an Agent for Change, a Fund Raiser and I am beginning work on developing into a Patient Advocate role.

This disease has brought kind, resourceful, strong-willed and inspiring people into my life for which I am enormously thankful. However, GNE myopathy has a devastating ripple effect on loved ones around us. Not everyone has the mental stamina nor the support around them to cope with this condition. As patients, we are desperate - especially now because we are so close to a treatment for this rare condition. Our GNE myopathy community and their families struggle with the long and complex wait for treatment to be approved and are very grateful to companies such as Ultragenyx who are investing into research and thus providing light at the end of the long, sometimes dark tunnel. I hope that before long, a treatment will be made available so that no one has to suffer the painful life experiences that are brought about by living with GNE myopathy.

Looking forward and spreading awareness

Over the last year I have been involved in various fundraising campaigns (the London Duathlon and the London to Paris Bike Ride) which have aimed to raise awareness about rare genetic diseases in the public domain, support new initiatives to bring existing research from the lab to the patients and to develop accurate methods to reduce the frequency of misdiagnosis. I am also in the process of becoming involved in a patient advocacy role with Muscular Dystrophy UK (MDUK).

Patient Power

I'm pleased to see that the GNE myopathy patient community is taking control and collectively driving forward important changes. Raising awareness of the disease via methods such as social media campaigns, charity work, disease specific webinars and patient days have all been successful. All these initiatives help to eliminate the isolation, remove hurdles, and provide vital support to each other and our caregivers. More importantly, it inspires and empowers us to keep pushing ourselves and never give up hope.

Thank you for taking the time to read my story. Mona



London Duathlon 2016
'You care because I'm rare'