FSHD Advocate

2018 • ISSUE 3

FSH SOCIETY
FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

SUPERHEROES!
Our Inaugural Walk & Rolls raise over $230,000
See page 10

Small but mighty kids in capes at the Pacific Northwest Walk & Roll

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FSHD Advocate

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CEO Letter

FSHD ADVOCATE— Championing faster treatments, stronger lives

Did you notice? Of course you did! Our newsletter has gone through a metamorphosis. Due to the superb quality of the content we have all enjoyed (kudos to June Kinoshita, our chief strategic programs officer and editor-in-chief), we began to investigate transitioning to a magazine format. Amazingly, we discovered we could upgrade the format while lowering the cost of production (a very important criterion), so we decided it is time to refresh our periodical.

Along with a new format, we considered a new name. We turned first to the staff and executive committee who developed and narrowed a list from more than 20 titles down to a half-dozen, including the option to keep the name unchanged. After this exercise, we asked many of our volunteer leadership, board, and chapter directors to vote on names they liked. The clear winner was *FSHD Advocate*.

FSHD Advocate speaks to the agenda that underlies everything we do to educate and empower our community, and to accelerate the development of treatments. We honor your advocacy, which you achieve through your donations, volunteer efforts, and leadership, by amplifying your stories and celebrating your efforts—the research advances, community-building, fundraising victories, and personal triumphs.

FSHD Advocate communicates the sense of urgency we feel at all levels of the FSH Society to get treatments to our families faster. It reflects our focus on building a global collaborative to lead the way to effective treatments by the most efficient route possible.

Mark A. Stone

FSHD Advocate engages our community by telling you how, when, and where you can become involved in research studies and clinical trials, chapter meetings, Walk & Rolls, and other ways to make an impact.

FSHD Advocate celebrates our families who are overcoming obstacles, living purposeful lives, and making a difference by actively participating in the FSH Society community.

Most of all, *FSHD Advocate* connects all of us—families and friends, clinicians, researchers, drug developers, FDA regulators, and funding agencies—so that your voice, multiplied with and magnified by others, can change the world.

On behalf of the patients and families we serve, thank you for your continued support of our common mission—a cure for FSHD. With your help, we can move that dream closer to today.

Mark

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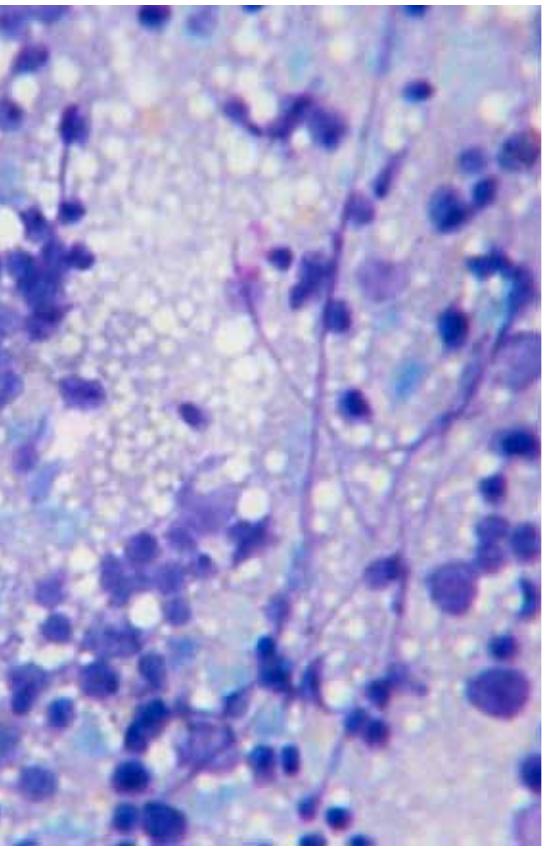
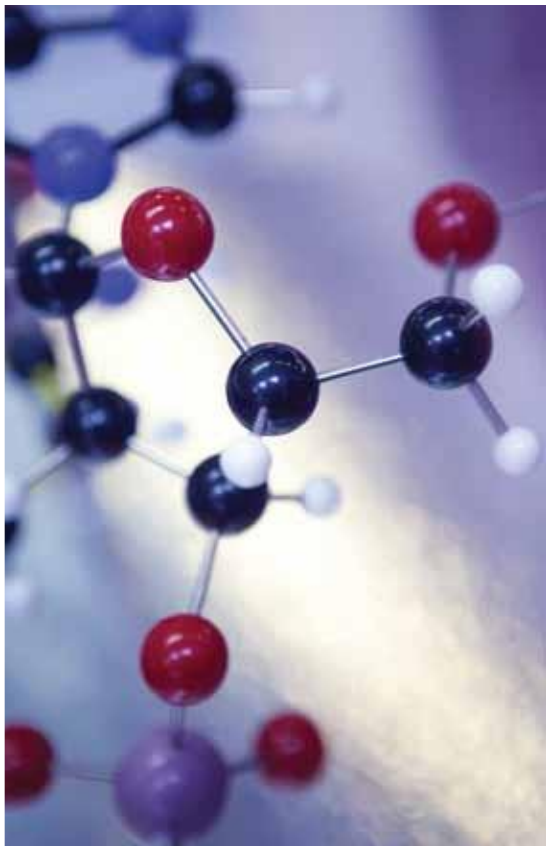
FSH Society latest grant awards

Regenerative therapy, DUX4 trap, and why females have an edge

BY JUNE KINOSHITA AND DANIEL PAUL PEREZ, FSH SOCIETY





One of the blue-sky dreams for those of us working toward treatments for FSH muscular dystrophy is regenerative therapy—treatments to generate healthy muscles to restore or replace those damaged by disease. We have taken an important step toward realizing this dream with our latest grant award for a project that will test stem cell therapy in a mouse model of FSHD.

A second award goes to a new tactic to prevent DUX4 protein from setting off a series of deleterious events that lead to muscle cell death. The third grant given out in this cycle takes aim at a prevailing mystery—why males (on average) develop symptoms a decade earlier than females. Unraveling this secret could point the way to treatments that harness the mechanisms that help slow down the disease process in women.

These proposals, representing a total commitment of $388,445, were received for the February 2018 cycle of grant submissions and approved at the Society's Board of Directors Meeting on September 25, 2018. Here are our latest grant awards:

- **Determining the therapeutic potential of pluripotent stem cell-derived myogenic progenitors in the iDUX4pA mouse model**


Rita Perlingeiro

Rita Perlingeiro, PhD, University of Minneapolis, Minnesota, USA

US$99,998 total (US$49,999 annually for two years)

There has been tremendous excitement for the therapeutic potential of induced pluripotent stem (iPS) cells in treating genetic diseases. These cells are derived from patients' skin cells, which are genetically "reprogrammed" to become stem cells, with the ability to develop into muscle. This project builds on the Perlingeiro lab's successful studies developing such cell therapies specifically in mouse models of Duchenne and limb-girdle muscular dystrophy (LGMD).

The intent of this cell product is to replace diseased muscle with normal functional muscle fibers as well as muscle stem cells, which have the potential to provide long-term therapeutic effect in Duchenne and other devastating types of muscular dystrophies, including FSHD. Because all of the Perlingeiro lab's work to date has been with Duchenne and LGMD models, it will be essential to understand how effectively cell replacement can address muscle damage due to the distinct mechanism underlying FSHD.

Now that an FSHD mouse model (iDUX4pA) is available that can be induced to produce very low levels of DUX4, resulting in a slow decline in muscle over several months, it will be possible to evaluate the effectiveness of cell therapy in the context of such a relevant muscle damage mechanism. The work proposed in this grant will provide proof of principle for including FSHD in the pipeline for future clinical trials of cell-based regenerative therapies.

- **A decoy trapping DUX4 for the treatment of facioscapulohumeral muscular dystrophy**


Virginie Mariot

Virginie Mariot, PhD, University College London; Great Ormond Street Institute of Child Health, London, UK

US$163,447 for 18 months

Nearly 20 laboratories (including Drs. Mariot's and Dumonceaux's) have proposed therapeutic approaches for FSHD, but no one can predict whether any of these approaches will be successful in human patients. It is therefore important to continue to develop new strategies. This application uses a "decoy" approach, which represents a new conceptual approach in the neuromuscular field.

Unlike antisense oligonucleotides (ASO/AO) or siRNAs which target DUX4 messenger RNA (mRNA) prior to the creation of the DUX4 protein, the decoy mechanism of action is to trap the DUX4 protein itself. The decoy will attach to the DUX4 protein so that it cannot bind to DNA and trigger the downstream toxic effects of DUX4. This decoy strategy may be highly powerful as shown by proof-of-principle studies already performed. The aim of this project is now to validate these results in the FLEx ACTA MCM mice.

- **The role of estrogen receptors in FSHD-1 mechanism**


Anna Pakula

Anna Pakula, PhD, Boston Children's Hospital, Boston, Massachusetts, USA

US$125,000 for one year

FSHD individuals with shorter D4Z4 repeats are reported to be more severely affected, but there is still an unsolved conundrum on different disease manifestation in women and men. Sexual dimorphism in FSHD has been studied among American, Brazilian, Italian, and Dutch FSHD patients. Clinical (e.g., MRI) and neurological data revealed that in these populations, men manifest the disease earlier in their life and are more severely affected than women. The underlying mechanism explaining these noticeable sex differences in disease severity remains yet unsolved and will be the goal of these studies.

Dr. Pakula utilizes fish embryos, which when programmed to synthesize Dux4, develop features that resemble FSHD symptoms. This model is helpful for studying the mechanism and potential treatments of this disease. By performing analysis of DUX4 binding sites they have discovered that, at 12 hours of embryo development, estrogen receptorlike protein interacts with DUX4. In this way, DUX4 and estrogen receptor interaction can be detected at the very early stages of disease development, which is not feasible in humans.

The investigators hypothesize that one of the estrogen receptors could help DUX4 reach its binding sites in DNA. Their hypothesis is that in males (having less estrogen than females), DUX4 binds to different DNA regions and regulates different genes, which possibly leads to more severe disease.

Drs. Kunkel and Pakula, together with Drs. Martha Bulyk and Yuliya Sytnikova from Brigham and Women's Hospital, who are well established in studying transcription factors and chromatin, will unravel the mechanism of ER-like driven recruitment of the DUX4, which they believe may help to uncover new ways to treat FSHD.

EDITOR'S NOTE

The FSH Society funded the development of the zebrafish, the FLEx mouse, and characterization of the iDUX4pA mouse models used in these projects.

The use of antioxidants in FSHD

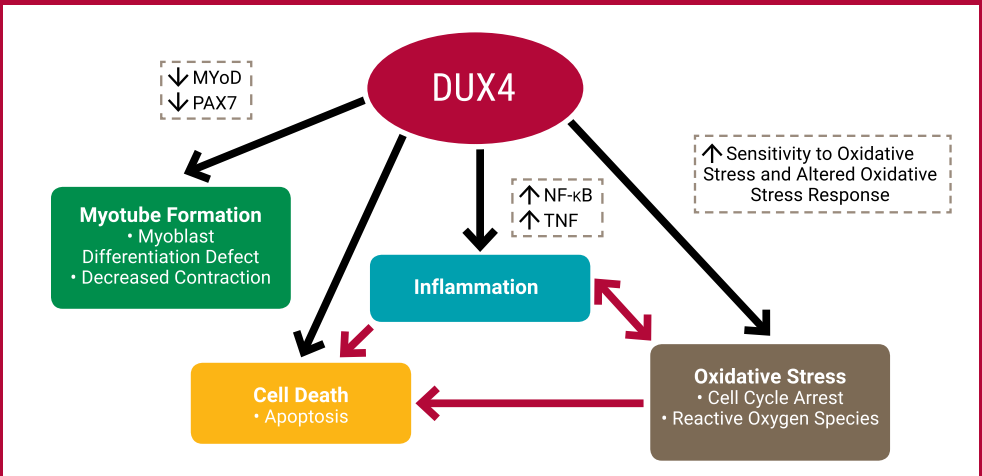
What is the scientific rationale and what does the evidence show?

BY ADAM DENNY, PHD, DUNEDIN, NEW ZEALAND

In recent years, scientists around the world have begun to investigate the role of oxidative stress in FSHD. A 2018 study reported that muscle biopsies from people with FSHD had greater levels of oxidative stress markers when compared to healthy control muscle (Dias Wilson et al., 2018). In another study, a stem cell-based model indicated that high oxidative stress itself can lead to increased DUX4 expression (Sasaki-Honda et al., 2018).

Lab studies have shown that DUX4 expression can induce a multitude of problems within skeletal muscle:

- **Impairs the correct formation of skeletal muscles (myotube formation).**
- **Increases inflammation, oxidative stress, and cell death (black arrows).**
- **Both inflammation and cell death can increase the levels of each other (double-headed red arrow).**
- **Both oxidative stress and inflammation can further increase levels of cell death (red arrows).**



These findings indicate that DUX4 can increase oxidative stress, and that oxidative stress itself can increase DUX4 expression, proposing a damaging feedback loop, although this hypothesis needs further investigation.

What is clear in FSHD is the imbalance in reactive species and antioxidant defenses, the two key aspects underpinning oxidative stress.

What is oxidative stress?

Oxygen is essential to life, but it's a double-edged sword. Certain oxygen-containing molecules are chemically very reactive and, if allowed to run amok in our bodies, can damage DNA, proteins, fats, and other components. To combat these "reactive species," biology has evolved molecules called antioxidants that neutralize or repair the damage.

Oxidative stress results when the production of reactive species outpaces the body's antioxidant defenses. This imbalance can result in long-term damage. Increases in oxidative stress are beneficial in some circumstances, for example, to destroy cancer cells, but in disease, oxidative stress can be harmful.

The role of oxidative stress in FSHD

Most studies of FSHD and oxidative stress are conducted in laboratory models, so we have to be cautious about extrapolating these findings to humans.

As depicted in the figure (above), lab studies have shown that DUX4 expression can induce a multitude of problems within skeletal muscle.

These include impaired formation of muscle cells and increased inflammation, oxidative stress, and cell death.

Given these lab findings, individuals with FSHD may well wonder if they should take steps to reduce the potential harm from oxidative stress.

About antioxidants

To combat oxidative stress, we have antioxidants—substances that can

delay, prevent, or remove oxidative damage.

There are two categories of natural antioxidants: enzymatic and non-enzymatic antioxidants. Enzymatic antioxidants are produced by our bodies and work through breaking down and protecting against the reactive species. Non-enzymatic antioxidants are a much larger class of antioxidants and work through disrupting the chemical reactions caused by reactive species.

Some natural non-enzymatic antioxidants are made within our bodies, such as vitamin A and coenzyme Q10. When our bodies don't make sufficient amounts, we can take them in pill form. Others stem from external sources, such as vitamins C, E, and K, along with zinc and selenium.

Antioxidants from external sources are important to factor into a person's diet. While these antioxidants are also available as pill supplements, many people prefer to obtain these antioxidants from a balanced diet.

Antioxidant trials

While antioxidants have shown promise throughout the years in laboratory studies, these results have been hard to replicate in clinical trials.

One clinical trial investigated the effect of combined dietary supplementation of vitamins C and E, and minerals zinc and selenium in individuals with FSHD (Passerieux et al., 2015). The researchers found that supplementation did not improve the two-minute walk test, but it did improve muscle function: individuals could contract their thigh muscles (quadriceps) harder and for longer than they could before the supplementation.

The participants who received supplementation also saw decreases in some of their oxidative stress markers and increases in certain markers of their antioxidant defense system.

In another small clinical trial, a Dutch group (Van der Kooi et al., 2016) investigated the supplementation of folic acid and methionine in people with FSHD. Both supplements have antioxidant properties, and folic acid has previously been shown to boost DNA methylation, but this study found neither folic acid nor methionine had an effect on DNA methylation levels.

Other ways to protect against oxidative stress

Exercise is a very effective way to increase our antioxidant defenses. However, in order to obtain this benefit, one has to first use exercise to increase levels of oxidative stress. The body then responds by boosting its antioxidant defenses.

While the oxidative stress produced in exercise is vital, the exact effect this may have on FSHD is not fully understood. The type, intensity, and duration of the exercise all may influence the outcome.

Bankolé and colleagues (Bankolé et al., 2016) have shown that a combined strength and interval cycling exercise-training program significantly improved fitness and skeletal muscle function without negatively impacting muscle damage. While this study did not investigate the antioxidant levels of participants, it does highlight that certain types of exercise can be beneficial for people with FSHD regardless of the increases in oxidative stress induced by exercise.

In conclusion...

Research to date has shown some positive results, but important questions remain. First, oxidative stress has a strong link with FSHD cells in the test tube, but the relevance of oxidative stress in FSHD patients is unknown.

Also, while antioxidant therapies have shown modest benefits, these results came from relatively small clinical trials. We need to conduct larger trials to understand if antioxidant therapies can protect muscles in people with FSHD.

EDITOR'S NOTE

Adam Denny earned his PhD in the Department of Physiology at the University of Otago in New Zealand.

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DUX4 vs. PAX7

Who's the fairest one of all?

BY AMANDA HILL
HIGHLANDS RANCH, COLORADO

For several years, DUX4 has enjoyed center stage in the yet-unfolding story of facioscapulohumeral muscular dystrophy (FSHD). DUX4 was first identified in 1999[1], but only in the past five to 10 years have scientists reached consensus about the full underlying genetics of FSHD. Since then, researchers have worked tirelessly to understand how DUX4 causes muscle toxicity and cell death[2], and how it prevents muscle regeneration.

Recently, however, a Snow White-like story is unfolding, and scientists are starting to pay attention. While no one questions the foundational role of DUX4 in the pathogenesis of FSHD, three separate groups of researchers are now also calling attention to a protein called PAX7 and its close cousin, PAX3. It seems that DUX4 is like the evil, jealous stepmother who banished and put to sleep the "fairest one of all"—the kindhearted princess, PAX7.

Both DUX4 and PAX7/3 are members of a family of proteins known as "transcription factors." Transcription factors bind DNA to regulate expression of genes that are important in embryonic development and in differentiation of cells into specific tissues. PAX7 and PAX3 are key regulators of the formation of skeletal muscle, though PAX3 generally operates during embryonic development while PAX7 generally operates later in development and in adult muscle regeneration[3]. In our Snow White story, PAX7 is the princess that everyone wants to see prevail.

About 10 years ago, Darko Bosnakovski, DVM PhD, and Michael Kyba, PhD, then at the University of Texas Southwestern Medical Center, discovered that in a cell culture model of FSHD, the presence of DUX4, the evil queen, causes the function of PAX7 to be suppressed. When researchers manipulated the cells to artificially increase expression of PAX7, the FSHD cells survived more robustly. This indicated that the function of PAX7 may somehow counter the deleterious effects of DUX4[4].

Last year, these studies were resurrected and greatly expanded upon. A team at the University of Washington led by Daniel Miller, MD PhD, found that in early development, FSHD stem cells have normal expression of both PAX7 and PAX3 as they differentiate into muscle cells, consistent with the observation that most children with FSHD have normal muscle development and growth. Interestingly though, DUX4 expression was not observed at the predicted rates in individual cells also expressing PAX7 or PAX3. This indicates that in early development, conditions promoting PAX7/3 expression may counter DUX4 expression, and that expression of DUX4 and PAX7/3 may be mutually exclusive[5].

In parallel, Christopher Banerji, PhD, and Peter Zammit, PhD, at King's College London reanalyzed several gene expression datasets previously generated from muscle biopsies from patients affected by FSHD. They found that the *suppression* of PAX7-regulated genes is, in many instances, actually a stronger and more reliable biomarker of FSHD than the *expression* of DUX4-regulated genes.

The network of genes regulated by PAX7 and suppressed in FSHD could also explain many FSHD phenotypes, including less effective antioxidant properties, cell death, inability to regenerate muscle, and the expression of DUX4 itself. These researchers also manipulated healthy cells to co-express both DUX4 and PAX7, and found that they mutually inhibited each other's ability to activate their target genes[6].

However, exactly how DUX4 and PAX7 interact remains to be deciphered. It seems that the relationship between the two is more complex than a simple, direct competition model would suggest[7]. Some non-mutually exclusive hypotheses that have been put forth include: **1)** DUX4 and PAX7 compete to bind DNA at a few key toxicity-related sites, and/or **2)** DUX4 and PAX7 compete to interact with a third, yet-unknown protein necessary for their activity, and/or **3)** DUX4 may interfere with the DNA-binding capabilities of PAX7.

I hope that at this point you can appreciate how DUX4 and PAX7 seem to have an antagonistic, seesaw-like relationship. As Drs. Banerji and Zammit explain, it appears that DUX4 operates in two ways to cause FSHD: **1)** by direct activation of certain genes that results in muscle cell death (the evil queen is simply toxic), and **2)** by suppressing the work of PAX7, such as in muscle regeneration (the evil queen puts Snow White to sleep). In theory, if Snow White were awake, she may help counter the toxic effects of the evil queen.

It is clear that scientists are just starting to get to know PAX7, our Snow White, and what role she plays in the FSHD story. And understanding PAX7 biology is valuable because it may shed light on additional therapeutic opportunities. We'll continue to watch this Snow White and the evil queen storyline unfold with great interest, as it will inevitably lead to an even greater understanding of FSHD pathogenesis, and may help contribute to a more "happily ever after" for FSHD sufferers.

FOOTNOTES

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Freedom through AFOs

Finding the right one for you is worth the effort

BY ROD FULMER, MCDONOUGH, GEORGIA

Rod Fulmer visits Jerry Lewis' star on the Hollywood Walk of Fame.

Who wants to wear ankle braces? I wish I didn't have to wear any, but because I need them, I'm glad I found carbon fiber braces that have worked very well for me. Mine are made by Allard USA, and I discovered them somewhat by accident.

My sister and I were sitting in a hospital waiting room one day when she leaned over and said, "Look at my new braces." I looked down to see these sleek and very light ankle braces. I convinced her to let me try them on, and to my amazement, with these braces on, I was able to walk easily up and down the hospital hall.

You see, just before this I had fallen badly in the parking lot of the grocery store. To this day, I cannot tell you why I had gone to the grocery store that day. All I recall was that I needed to get home because I had fallen, and I could feel the blood running down my legs. At the time, I wasn't using AFOs (ankle-foot orthoses).

That day in the hospital with my sister was not my first encounter with an AFO. I had previously been custom fitted with hard-plastic, hinged monster braces, but they ended up in my closet. They were horrible—heavy, and rigid. The reason I needed AFOs is because I have FSH muscular dystrophy, which gave me foot drop and made me prone to falling. Falls are very dangerous. You never know what you will break or hit; plus there's the embarrassment of it all.

Having tried my sister's carbon fiber braces, I couldn't wait to get a new prescription for myself. Now, eight years later, I am still wearing them. Thanks to how lightweight the brace is and how it helps to lift my foot, I am able to walk much farther without getting tired than I ever could with my old, plastic AFOs. This is a key point, because when you have FSHD, it is important to remain as active as possible to keep muscles from deteriorating.

A few weeks ago, we took a trip to Los Angeles, and thanks to my Allard AFOs, I was able to walk the Hollywood Walk of Fame and see the many stars, one of which honored a man who is a hero to many of us with muscular dystrophy—the late Jerry Lewis.

I can't tell you what AFO is right for you because there are many different brace manufacturers and types. I can only tell you what has worked for me.

Please, if you are considering braces, do some research, compare and ask about warranty, and consult a good orthotist. Here are a couple of websites that are good places to start: *https://www.cmtausa.org/resource-center/treatment-management/bracing/ and www.getbackuptoday.com.*

EDITOR'S NOTE

Rod Fulmer is a senior purchasing agent for Dodson Global, Inc., and since 2013 has been a brand ambassador for Allard USA.

Finding beauty in disability

I am a creator of art, ideas, and dreams

BY AUBRIE LEE
LOS ALTOS HILLS, CALIFORNIA

I have a disability. It has manifested differently throughout my life, I have felt differently about it in various stages of my life, and people have treated me differently my whole life because of it.

I could walk when I was a child, and I transitioned to using a wheelchair over my teenage years. Now, I'm an adult (or so they tell me), and soon I will have spent more of my life with a wheelchair than without one.

It's funny—as my disability became more pronounced, I became more comfortable with it. That has been my journey.

Now I want to bring others on that journey. I want to bring you on that journey. My disability is not all of me, but I would not be who I am without it. It's not bad. It's different. It's notable. In fact, it's even … no, could it be? Dare I say it? Beautiful.

What is beauty but the quality that beholders' minds decide? Behold me. I am temporary flesh and durable machine. I am an index for the progression of society. I am a creator of art, ideas, and dreams. I am a glimpse of your future. I am a person whom friends and family love no less. I am a case study in the possible. I am one who can behold the world and treasure it.

And I am not the only one.

So when you think of disability, I want you to think of the beauty in it.

***Nobility*, by Aubrie Lee.**

INAUGURAL WALK & ROLL CAMPAIGN:

A tremendous success!

More than $230,000 raised by our first five events

BY LEIGH REYNOLDS, KANSAS CITY, KANSAS

When we began planning for the inaugural Walk & Rolls to Cure FSHD, a $105,000 fundraising goal felt ambitious. Then an incredible group of volunteer leaders stepped up to pioneer this national campaign in five communities across the US. They worked tirelessly to make magic happen, and their dedication, drive, and determination led to remarkable results!

- More than $230,000 raised by walks from coast to coast: Colorado, Ohio, California, Washington State, and North Carolina.
- 542 walkers representing 67 teams.
- Thousands reached with the story of FSHD, increasing awareness and understanding.

I've worked to launch walks with other groups across the country with similar standards. Your inaugural walk is one of the strongest volunteer-driven campaigns I've seen.

So many things went into the success of this event—tremendous volunteer leaders, a growing army of engaged walkers and fundraisers, corporate supporters, and staff leadership.

Also playing a pivotal role was our investment in the technology needed to support it all. Our peer-to-peer system made it easy for individuals and teams to share personal stories with their friends and family and to enlist them to fundraise on their behalf.

"The Colorado Walk & Roll is a great testament to how powerful the peer-to-peer fundraising platform is," said Katie Ruekert, who founded the Colorado event three years ago.

Thank you to our volunteer leaders for making this all possible!

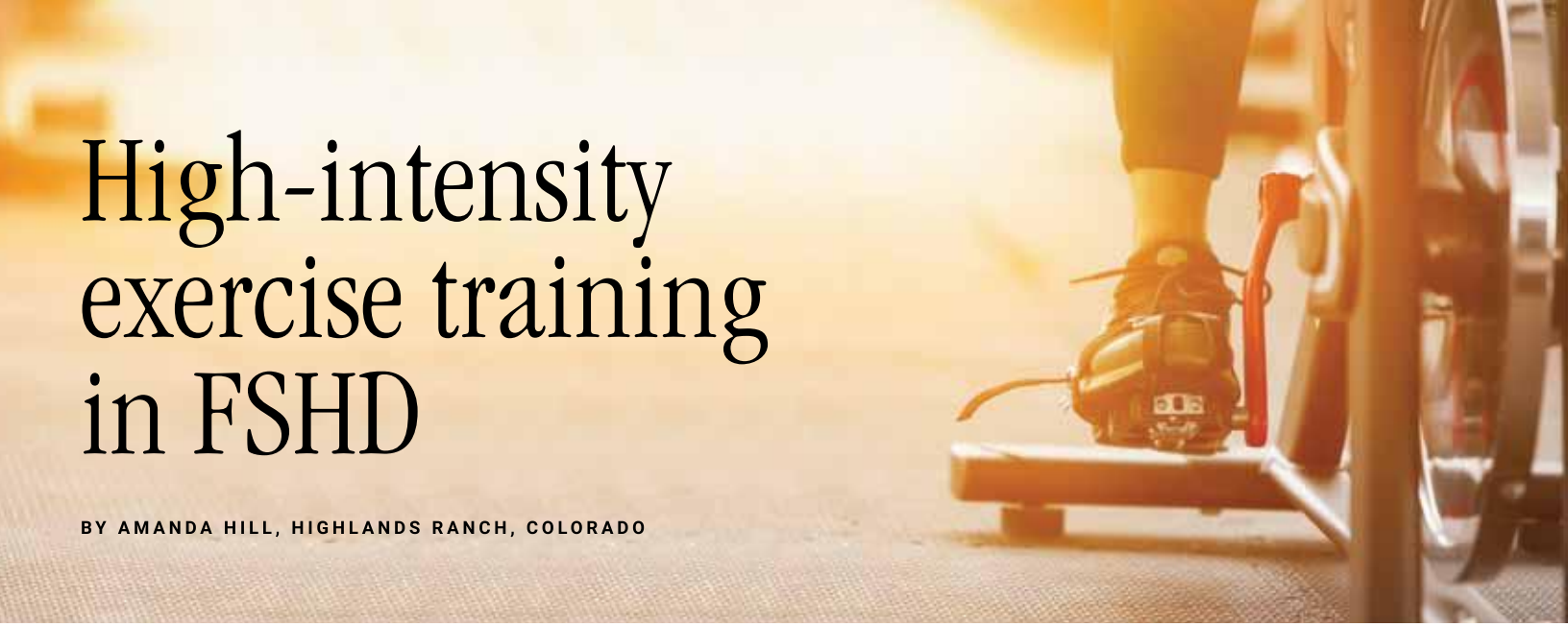
Rain or shine, walkers and rollers of all ages turned out more than 500-strong across the US and raised nearly a quarter-million dollars! Elizabeth Gerhard of OH Heavenly Bakes created special (and delicious) cookies for the Columbus Walk & Roll.

"During our first two years, we used a different fundraising model which included a registration fee. Our first year we raised $21,000, and in our second year we raised $32,500. This year, with the peer-to-peer technology, our participants set up their own teams to raise more funds, and we doubled what we raised to over $67,000!

"In addition to doubling the amount we raised, we doubled the number of participants and reached that many more families," Ruekert added. "It has been magical to see not only our Colorado Walk & Roll grow, but also witness the expansion of other Walk & Rolls across the country."

We couldn't be prouder of this growing community of activists, and we can't wait to bring this movement to more communities next year and make an even greater impact as we drive toward treatments to families by 2025!

If you want to be a part of this movement, contact Beth Johnston, chief community development officer, at *Beth.Johnston@FSHSociety.org*.



High-intensity exercise training in FSHD

BY AMANDA HILL, HIGHLANDS RANCH, COLORADO

If you or a loved one is affected by FSHD, or any muscular dystrophy for that matter, chances are that you've heard it's best not to exercise, just to avoid damaging or "using up" what healthy muscle is left. There is a pervasive uncertainty and fear among patients and doctors alike that exercise may accelerate disease progression by adding excess strain to the muscles. As far as we can tell, this attitude was spurred by a series of three studies in a mouse model of Duchenne muscular dystrophy in the early 1990s, where results were conflicting as to whether exercise was beneficial or detrimental[1].

In more recent years, however, multiple well-designed and controlled clinical trials in FSHD—which has a very different disease mechanism than Duchenne—have made it the best-characterized type of muscular dystrophy with regard to the effects of exercise.

What are these studies showing thus far? In FSHD, *aerobic* exercise is a safe and effective way to increase oxygen uptake and endurance, and to reduce fatigue[2].

Recently, a group of clinicians at the University of Copenhagen, led by John Vissing, MD PhD, had the idea to take these observations a step further and evaluate high-intensity training (HIT) in people with FSHD Type 1[3]. HIT is a type of aerobic training carried out at an intensity level that maximizes the subject's oxygen uptake.

Vissing and his team decided to test an HIT regimen that they adapted for individuals with FSHD to perform on a stationary bicycle. The regimen was 21 minutes long and consisted of an eight-minute warmup, followed by two sets of five-minute HIT with a three-minute break of low-intensity pedaling in between. The HIT portion of the regimen was carried out in 60-second intervals where 30 seconds were spent at low intensity, 20 seconds at moderate intensity, and 10 seconds at maximal-intensity pedaling. Individuals in the study performed this exercise regimen three times per week for eight weeks.

Notably, no episodes of muscle damage were reported, and creatine kinase levels (a marker of muscle damage) remained unchanged, indicating that the HIT regimen did not have a detrimental effect on muscle or speed up the progression of FSHD. Also notable, the FSHD individuals who performed the HIT regimen did not have an increase in fatigue, on average.

Vissing's team also evaluated a variety of other measures of overall fitness and strength before and after the eight-week regimen. They found that HIT training increased maximal oxygen uptake and the maximal pedaling power the participants were capable of achieving, indicating that overall fitness and endurance were improved. Other standard tests used to measure FSHD progression, like the six-minute walk test and the hand dynamometer, were unchanged by the HIT regimen.

While this particular study was small, it adds to the increasing body of evidence that aerobic exercise is safe, and even beneficial, in people with FSHD. More specifically, HIT improves overall fitness without increasing fatigue or damaging muscle. And, as it turns out, HIT was preferred by the participants over other forms of training.

If you are interested in starting an HIT routine, you should speak with your doctor or a physical trainer to ensure you select a safe and appropriate regimen.

FOOTNOTES

[1] Petrof BJ. (1998). The molecular basis of activity-induced muscle injury in Duchenne muscular dystrophy. *Molecular and Cellular Biochemistry.* 179(1-2):111-124.

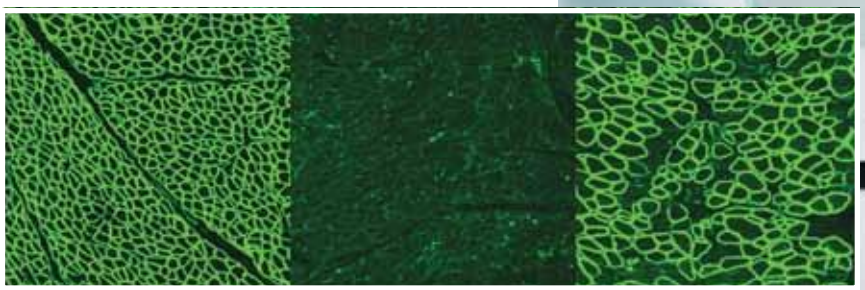
[2] Preisler N, Orngreen MC. Exercise in muscle disorders: what is our current state? *Current Opinion in Neurology.* 2018;31(5):610-617.

[3] Andersen G, Heje K, Buch AE, Vissing J. High-intensity interval training in facioscapulohumeral muscular dystrophy type 1: a randomized clinical trial. *Journal of Neurology.* 2017;264(6):1099-1106.

Gene editing takes big step forward

Proof of concept in Duchenne dog model

BY JUNE KINOSHITA, FSH SOCIETY



Scientists used CRISPR gene editing to halt the progression of Duchenne muscular dystrophy (DMD) in dogs. The images illustrate dystrophin (in green) in a healthy diaphragm muscle (left), absence of dystrophin in a dog with DMD (center), and restoration of dystrophin in dogs treated with CRISPR (right). Photo courtesy of UT Southwest.

Researchers at the University of Texas Southwestern Medical Center in Dallas announced that they have made a significant advance in demonstrating the possibility of using CRISPR gene editing technology as a therapy for Duchenne muscular dystrophy (DMD).

The technology was designed to "patch" a mutation in the dystrophin gene, which is defective in DMD, and put it into the adeno-associated virus (AAV, related to the common cold virus). The virus delivered the genetic "patch" into the muscle cells of dogs that have the DMD mutation and was able to restore production of the dystrophin protein. This is the first demonstration of the effectiveness of this approach in a large animal model of Duchenne.

What is the significance for FSHD? It has been shown previously that the CRISPR method can fix the DMD defect in cells and in mice, but this study demonstrates that the gene therapy can be delivered into muscles and organs of a large animal and correct the genetic defect at a level that should provide a therapeutic benefit.

A related approach is being developed for FSHD by Charis Himeda, PhD, of the University of Nevada, Reno. She has cleverly harnessed CRISPR technology to repress the DUX4 gene in adult muscle.

Significant challenges remain. The AAV "vehicle" can trigger a potentially dangerous immune response in patients (because most adults have been previously exposed to AAV). And there is currently no large animal (dog or primate) model for FSHD in which to demonstrate safety and proof of principle for this technique.

Yet there is significant excitement about the potential for using CRISPR approaches to manipulate gene expression to treat diseases, with growing numbers of companies entering the space, so stay tuned!

Eric Olson, PhD

REFERENCE

Amoasii L, Hildyard JCW, Li H, Sanchez-Ortiz E, Mireault A, Caballero D, Harron R, Stathopoulou T-R, Massey C, Shelton JM, Bassel-Duby R, Piercy RJ, Olson EN. Gene editing restores dystrophin expression in a canine model of Duchenne muscular dystrophy. *Science*. 2018 Oct 5;362(6410):86-91.

Revenge of the NuRD

Study uncovers new proteins involved in regulating FSHD-linked gene

BY RACHEL TOMPA, FRED HUTCH NEWS SERVICE

A new study has revealed more players in the pathway of facioscapulohumeral muscular dystrophy, or FSHD, the most common form of muscular dystrophy.

Amy Campbell, PhD

Led by Fred Hutchinson Cancer Research Center biologist Stephen Tapscott, MD PhD, and staff scientist Amy Campbell, PhD, the study, published in the journal *eLife*, is the first to systematically identify proteins involved in repressing the FSHD-triggering gene, DUX4.

Normally, the DUX4 gene is only turned on in very early embryonic development, shutting off before the embryo even implants in the uterus. But in people with FSHD, the DUX4 gene comes back on, progressively destroying muscle cells. The researchers have been trying to figure out how to shut it off again in hopes of finding new therapeutic targets that could halt that progression.

In their latest study, they used a CRISPR-based proteomics technique to find proteins that attach to the DUX4 gene and its neighboring DNA. They then asked whether those proteins are involved in shutting off the gene in muscle cells and in embryonic stem cells. Those experiments identified two large groups of proteins involved in shutting off, or repressing, DUX4, called NuRD and CAF-1. Tapscott and his colleagues then went on to identify a protein that represses those repressors, known as MBD3L2, which they believe

could be a potential new therapeutic target for FSHD.

The disease, which afflicts nearly 900,000 people around the world, is caused by an uncommon quirk of DNA. A genetic disease, FSHD is not triggered by a mutation in a gene in the way we might normally think about an inherited condition. Rather, it's caused by having too few copies of a piece of DNA called D4Z4—healthy people have 11 or more copies of D4Z4 on chromosome 4; having 10 or fewer copies triggers FSHD. Having fewer copies of D4Z4 causes DUX4 to occasionally switch on when it shouldn't, wreaking havoc in skeletal muscles. It's not clear why DUX4 turning on is particularly damaging for muscle cells over other cell types, the researchers said. But their study points to a possible model for what could be going on.

In skeletal muscles, a single muscle fiber is made up of many muscle cells, but they've all fused together and lost the barriers between them. All their DNA-storage compartments, known as nuclei, are bundled together. Campbell and Tapscott think that in people with FSHD, the DUX4 gene may spontaneously turn back on only in a few cells at a time, but because muscle-cell nuclei don't have walls between them, DUX4 could "spread" its way from nucleus to nucleus along the muscle fiber, leaving destruction in its wake. In other cell types, if DUX4 turns itself back on, that cell would simply die without harming nearby cells.

"The environment is able to compensate for the loss of a single cell," Campbell said, "whereas in a muscle, you're affecting these large muscle fibers that maybe can't catch up."

The MBD3L2 protein that their study identified seems to be at least partly responsible for turning DUX4 back on, and they wonder if that protein could be responsible for the spreading—and the progressive nature—of FSHD. Those are still big unknowns, Tapscott said. "If the spreading from nucleus to nucleus is the basis of progression, then blocking the spreading by blocking MBD3L2 could slow down progression," he said.

Campbell also found that the NuRD and CAF-1 protein clusters shut DUX4 off in embryonic cells; next, they want to ask whether MBD3L2 is also involved in normal embryonic development in the same way it seems to be acting in FSHD muscle cells.

Additionally, DUX4 was recently found to be involved in some rare types of leukemia and sarcoma, although it's not clear if the gene is behaving in the same way in these cancers as it does in muscular dystrophy. Campbell and Tapscott are planning to address that question next.

This study was their first foray into using the specific CRISPR technique, known as enChIP, and they're excited to see what else they and their colleagues might discover with further similar studies.

"This approach worked, and we can go further with it," Tapscott said. "We can now go deeper into this data and deeper into this approach, perhaps for some of these [mutations] in cancer as well."

"This approach worked and we can go further with it. We can now go deeper into these data and deeper into this approach, perhaps for some of these [mutations] in cancer as well."

—STEPHEN TAPSCOTT, MD PHD,
FRED HUTCHINSON CANCER RESEARCH CENTER

EDITOR'S NOTE

The National Institutes of Health, the FSH Society, Friends of FSH Research, and Fred Hutch Reservoir Fund funded this study.

Rachel Tompa is a former staff writer at Fred Hutchinson Cancer Research Center. She has a PhD in molecular biology from the University of California, San Francisco, and a certificate in science writing from the University of California, Santa Cruz.

Have you pulled down your oxygen mask?

BY SUSAN W. AUMILLER, CLTC, DUBLIN, OHIO

Recently I was sitting next to my husband on a flight to Nevada. I had buckled my seat belt and was casually listening to the flight attendants delivering their safety message. When I heard them say that I should put on my oxygen mask *first*, before helping the person next to me, I gripped my husband's hand tightly. Nearly one year ago, both my husband and my son were diagnosed with FSHD. Our lives haven't been the same since then.

After our 36-year-old son, Bill, was diagnosed, I sobbed for months with breakdowns that came out of nowhere. Bill is a vibrant outdoor adventurer who lives in Colorado with his wife, Jamie, and our two grandchildren. I was heartbroken that FSHD might take away the activities he loved so much and that someday he might not be able to care for his family the way he wanted to.

Six weeks after Bill was diagnosed, my husband, Bob, was also diagnosed with FSHD. His test showed dystrophy (scar tissue) in every muscle of his body from his face down to his ankles and feet. We had never even *heard* of FSHD, and now it cast a deep shadow over our family.

Looking back, I am so grateful that Bob and I had purchased long-term care (LTC) insurance five years ago at ages 58 and 56. As a long-term care specialist, I was insistent because longevity runs deep in our family.

I never expected that my husband might need help from our LTC insurance policy before me. As his muscular disability progresses, I will not be able to lift or transfer him without hurting myself.

When we face a health crisis, we need to put into play realistic solutions not only for our loved one(s) who face a disabling condition, but also for ourselves. After Bob was diagnosed, I insisted on moving out of our home of 30-plus years and into a condo. I wanted to get that done while he could still help me with packing, lifting, and moving. He now has everything he needs on one floor, and there is less upkeep for us to manage.

Our son, Bill, is a certified financial planner. He had intended to purchase LTC for himself and Jamie when they turned 40. After the initial shock of his diagnosis, Bill called me to ask if there was any possible way for him to purchase that policy now. When I told him that he no longer qualified, he was devastated.

What made sense instead was to purchase an LTC policy for his wife. Bill knows that there is a chance he won't be able to help her as they age together. If Jamie needs care, an LTC policy would help pay for a home care provider to help with the heavy lifting. It would also pay for home modifications. The policy would pay for all levels of care, not only home care: assisted living, daycare, and nursing home care.

Buying a long-term care policy is like putting your oxygen mask on first—you're better able to take care of others when you take care of yourself first. For women, this is hard to do because we want to take care of the world. As for men, they typically don't think they will need help.

But we can't ignore or escape life's unexpected turns or the natural processes of aging—it happens whether we're ready or not. My advice is to pull down your oxygen mask first. Create a plan for the time when you or your loved one may need help with day-to-day activities.

Knowing you can pull out that policy and hire someone to handle the heavy lifting without disrupting the lives of your spouse, family, and friends will give you peace of mind. There is dignity as well, to have the ability to continue to live where you desire, with long-term care decisions made and costs covered.

Making a plan for long-term care and discussing it with your family is very important, especially if you expect your children to take care of you. After all, when was the last time they were in total agreement about anything?! If you are interested in learning more about long-term care and how to plan for it, I encourage you to contact a financial advisor.

Bob, Susan, and Bill Aumiller at the Columbus Walk & Roll to Cure FSHD.

EDITOR'S NOTE

Susan W. Aumiller, CLTC, is a financial professional and educator. She is director of the Columbus, Ohio, chapter of the FSH Society.

Frequently asked questions about long-term care insurance

Q At what age should a person purchase a long-term care insurance policy?

A Today, while you still qualify. Age 40 is a good starting point all the way into your 70s. There are annuities with tax-free LTC benefits available up to age 85. Calculations will show that paying lower premiums at a young age costs less in the long run than paying higher premiums at a later age.

Q What types of policies are available today?

A When LTC insurance first entered the market, they were mispriced and miscalculated. Today's policies barely resemble those old policies. New policies are now available that can offer a tax-free benefit whether you use them or not. These include:

- **Traditional** policies offering an LTC benefit that can grow with the cost of care through a compound inflation rider. A traditional policy can be very affordable. There is no cash value or death benefit if you never need LTC.
- **Hybrid** policies utilizing the death benefit from a life insurance policy. There are cash values and money-back guarantees. If you need care, you are able to access the death benefit while living and receive the benefits on a tax-free basis. If you never need care, more than the premium paid is reimbursed to your estate and your beneficiaries receive the death benefit tax free. If you change your mind and no longer want the policy, you can receive a return of the premium.
- **Annuities** for those who would use them for tax advantages and for those who may have a more challenging time qualifying for policies based on life insurance.

Q What is the impact of LTC insurance?

A *Prepared for America's Health Insurance Plans (AHIP) by LifePlans, Inc., January 2017.*

- 3 in 4 claimants indicated that without LTC insurance, they would receive less care.
- 64% said that without LTC insurance, they would be unable to pay for their current levels of care.
- 3 in 4 indicated their insurance enabled them to access higher-quality providers.
- Without LTC insurance benefits, 2 in 3 would have to rely on family, friends, and volunteers.

Scooting around unconscious biases

My journey has motivated me to work harder and develop a thick skin

BY MEREDITH MADDRY, ATLANTA, GEORGIA

Meredith Maddry (center) with her colleagues at DHG.

I have heard that to have an "executive presence" in business, one should stand tall, smile, and extend your arm for a firm handshake. Yet what if people in business can no longer stand, or smile, and are losing strength in their arms—should they give up the chance at a fulfilling career? That's not how I roll—pun intended.

My name is Meredith Maddry, and I work as a regional marketing manager for Dixon Hughes Goodman's (DHG) South region. I also happen to live with facioscapulohumeral muscular dystrophy (FSHD). You may have seen me riding my red scooter (aka "Big Red") around downtown Atlanta or through the lobby of One Ninety One Peachtree Tower. According to the United Nations, I am a member of the world's largest minority group—people with disabilities. However, in the business world, I often feel like a member of the smallest minority.

Living with a physical disability, which is the first thing people see about me before I can even introduce myself, I notice the unconscious biases surrounding me almost daily. Strangers assume I'm unable to work, and new industry acquaintances dismiss me as an influencer and leader, often directing their sales pitches to those standing tall around me.

I've been asked in our office building if I need directions after exiting our parking garage elevators, as if I must not actually work there. And a local Chamber of Commerce contact closed her pitch with a firm handshake and a "great to meet you" for my male and female co-workers, followed by an "it was lovely to meet you, sweetheart," for me … as if having a disability makes me a child.

Like other forms of muscular dystrophy, FSHD is a progressive disease, and I am truly grateful to my DHG team who have stood by me through my progression. I remember my first interview with DHG, when I walked into the office in three-inch heels and a pencil skirt. I also remember the last day I was able to wear three-inch heels, in 2009, when my co-worker drove me two blocks from our building to my car because I could no longer make the walk across the sky bridge. And I remember my first day entering our office with Big Red, which began the current chapter of my journey, as I was greeted at the entrance with a hug.

Though gaining credibility in the business world is a constant uphill battle, my journey has only motivated me to work harder and develop a thick skin. Do I work? The answer is yes … I manage a team and sometimes work 60+ hours a week. I also earned my MBA at Georgia State University in 2011 while working full-time. I work because I enjoy it, and because DHG was willing to take a chance on me, despite meeting my disability before meeting me.

EDITOR'S NOTE

With more than 16 years of experience in marketing and lead generation, including 13 years in DHG's Atlanta office, Meredith is the regional marketing manager for DHG's South region. A native of Miami, Florida, Meredith earned a bachelor's in business administration and marketing from the University of Georgia and an MBA with a concentration in organizational management from Georgia State University. Beyond DHG, Meredith enjoys cheering on the Dawgs, traveling, and spending time with her husband, Mica, and their temperamental Shih Tzu, Butters.

You are not alone

Driven by volunteers, supported by staff, the chapter program is our greatest opportunity to fund more research, connect more patients, and advance more progress

BY LEIGH REYNOLDS, KANSAS CITY, KANSAS

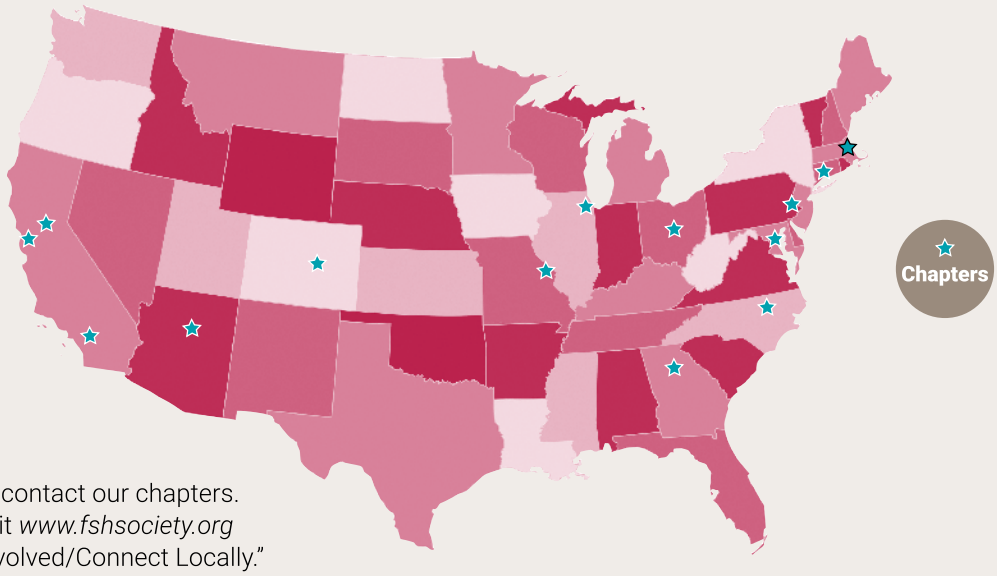
There is great power in community. When we come together, each bringing our own unique strengths and skills, we inspire each other to go further and reach higher than we ever could alone.

That's what the FSH Society chapter program is all about!

We want to celebrate our 14 inaugural chapters and their amazing volunteer directors. Their participation and leadership are paving the way for a stellar nationwide program that will build community, empower patients and their families, increase awareness of FSHD, and drive research progress. We are squarely focused on bringing treatments to families by 2025, and the Chapter Leaders are paving the way. This is just the beginning!

Our goal is to have at least 20 chapters by 2020. If you want to be a part of this movement, contact Beth Johnston, chief community development officer, *Beth.Johnston@FSHSociety.org*.

Building our "army of activists" chapter by chapter!



Here's how to find and contact our chapters. For an updated list, visit *www.fshsociety.org* and look under "Get Involved/Connect Locally."

New England—*fshsocietynewengland.org*
Kristin Zwickau— *NewEnglandChapter@fshsociety.org*

Connecticut—*fshsocietyCT.org*
Kathy Senecal—*CTChapter@fshsociety.org*

Greater Philadelphia Area—*fshsocietyphiladelphia.org*
Bill Maclean—*PhiladelphiaChapter@fshsociety.org*

Mid-Atlantic—*fshsocietymidatlantic.org*
Manuel Gomez—*MidAtlanticChapter@fshsociety.org*

Columbus, OH—*fshsocietycolumbus.org*
Sue Aumiller—*ColumbusChapter@fshsociety.org*

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Bay Area, CA—*fshsocietybayarea.org*
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Sacramento, CA—*fshsocietysacramento.org*
Karen Dunkerly—*SacramentoChapter@fshsociety.org*

Los Angeles, CA—*fshsocietylosangeles.org*
Laurie Heyman—*LosAngelesChapter@fshsociety.org*

Our new brochure for coping with an FSHD diagnosis

We have published a new e-brochure, "Not Alone," by Kelly Mahon Hessler. Based on interviews with a wide range of FSH muscular dystrophy patients, parents, and partners, this brochure, available online, assures those who have received a diagnosis that whatever they are feeling, others have had the same experience. We also provide resources for people to obtain information and find support, whether online or in person, from communities of fellow patients to professionals.

When people receive a diagnosis of FSH muscular dystrophy, they respond in ways that run the gamut of human emotions. For some, the initial shock of learning that they have a rare genetic condition may give way to relief that there is an explanation for their weird symptoms. For others, the news triggers grief, fear, or anger. Some people want to immediately learn everything they can, while others prefer to avoid any reminder.

These are all perfectly normal reactions. The important thing is to know that you are not alone. Talking to others who have been down this road can be reassuring. There are myriad ways to adapt. It can be equally validating to speak frankly to someone about your fears.

How did you respond when first diagnosed? What have you learned from your journey? What were the most (and least) helpful actions you took? Please share your story with us by emailing June Kinoshita at *june.kinoshita@fshsociety.org*.

"Not Alone" can be downloaded from our website's Library *(https://www.fshsociety.org/library/)*. We are deeply grateful to Kelly for taking on this important project.

Fulcrum Therapeutics raises $80 million


Robert Gould, CEO, Fulcrum

Fulcrum Therapeutics, the Cambridge, Massachusetts-based biotech that is developing a drug to treat facioscapulohumeral muscular dystrophy, announced that it has closed $80 million in series B financing.

The company hopes to have its initial public offering of stock early next year after filing papers with the FDA to begin human testing of its first drug for FSHD, according to Fulcrum's CEO, Robert Gould.

"We think that the strength of the preclinical data and the quality of the compound is such that it'll be an attractive investment opportunity," he says. Fulcrum's work was presented at the FSH Society's FSHD Connect Conference this past June by Dr. Lucienne Ronco. Her presentation can be seen on the FSH Society YouTube channel.

Fulcrum Therapeutics

Fulcrum reached out to patient groups to figure out which diseases to target even before the company was officially formed in 2016. That led it to the FSH Society. Since then, Fulcrum has worked with the FSH Society to understand the impact of FSHD on families and patients.

Through a program established by the FSH Society, the company also obtained muscle tissue samples from people with the disease who were undergoing surgery as part of their treatment. The company has used those samples to grow muscle cells from the tissue and test its drug candidates against those cells.

Correction to article on IRC, page 17 in *FSH Watch* 2018, Issue 2

FSHD2 is commonly caused by mutations in SMCHD1, a protein that silences repetitive DNA. Interestingly, mutations in this protein can also lead to arhinia, a rare developmental disorder characterized by the complete absence of an external nose. Several groups (Shaw, Talkowski, Van der Maarel, Van Engelen, and Blewitt labs) are now investigating how similar mutations in the same gene can lead to strikingly different diseases; their findings should aid the understanding and treatment **of both conditions.** (Was "both forms of FSHD.")

Be an FSHD hero—volunteer for research

We are more hopeful today than ever before that a treatment for FSHD is within sight. And there has never been a more important time to step up to the plate when research teams and companies put out a call for volunteers to participate in research studies. Your participation will without question help move us faster toward treatments and a cure.

Here are some of the ongoing studies that are seeking volunteers.

- Clinical Trial Readiness to Solve Barriers to Drug Development in FSHD. Jeffrey Statland, MD. Multiple sites in US.
- A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of ACE-083 in Patients with Facioscapulohumeral Muscular Dystrophy. Acceleron Pharma. Multiple sites in US.
- FSHD Biomarker Study. Wellstone Center for FSHD Research, University of Massachusetts Medical School. Robert Brown Jr., MD, and Larry Hayward, MD PhD.
- Research Study for FSHD (Facioscapulohumeral Muscular Dystrophy). University of Minnesota. Michael Kyba, PhD, and Peter Karachunski, MD.
- Research Study to Understand if the Resting Metabolic Rate and Cardiovascular Response to Exercise Are Affected by the Genetic Mutation That Causes FSHD. University of Minnesota. Manda L Keller-Ross, PhD DPT PT.
- Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Registry, Rochester, New York.

Visit our website (Get Involved/Enroll in a Clinical Trial) for additional studies and details.

Upcoming

Visit *https://www.fshsociety.org/events/events-calendar/* for updates.

CONFERENCES

November 10, Kansas City, KS
Kansas City FSHD Family Day Conference

WEBINARS

November 7, 12-1 p.m. US EST
Stephen Tapscott, MD PhD. Dr. Tapscott is among the world leaders in FSHD research. His lab studies gene transcription and expression in normal development and disease, including FSHD. Other research interests include gene and cell therapies for muscular dystrophy. He is a professor of neurology at the University of Washington School of Medicine and has an appointment at the Fred Hutchinson Cancer Research Center. Register online via our event calendar.

CHAPTER AND LOCAL MEETINGS

November 1, St. Louis, MO
St. Louis Chapter Launch

November 3, New York, NY
New York City Member Meeting

November 4, Worcester, MA
New England Chapter Meeting at Wellstone Center

November 11, Columbus, OH
Columbus Chapter Meeting

December 1, Los Angeles, CA
LA Connects Chapter Meeting

December 2, Palo Alto, CA
Bay Area Chapter Meeting

December 2, San Diego, CA
San Diego Member Meeting

VIRTUAL MEETINGS

Open to all!

FSH Society Talk Radio
broadcasts live on the last Wednesday of every month at 9 p.m. EST (8 p.m. CST). 2018 dates: November 1, November 28, December 26.

Connecticut Connections
meets via webinar on the first Thursday of each month (except in summer), 7-8:30 p.m. EST. 2018 dates: November 1, December 6.

Western Washington FSH Community
meets via Skype on the fourth Saturday of each month, 10-11 a.m. PST. 2018 dates: November 24.

FSHD Advocate

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info@fshsociety.org
www.fshsociety.org

YEAR-END CAMPAIGN:

The future is in powerful hands–YOURS

A cure is out there, and we are responsible for finding it. If we move swiftly to fund strategic projects, we will have treatments to our families by 2025. We will succeed—if every person who supports our mission makes a contribution. Whatever you can afford is deeply meaningful.

Our entire Board of Directors and additional generous benefactors have pledged $400,000 and challenge you to match it. Make your gift before midnight, December 31, 2018, to be counted toward the match. Thank you!

It's easy to donate:

- Give online at *www.fshsociety.org*.
- Call Kathryn Puzzanghera at (781) 301-7301.
- Mail a check using the enclosed envelope to the FSH Society, 450 Bedford Street, Lexington, MA 02420. This will save us credit card processing fees.