A Publication of the Facioscapulohumeral Muscular Dystrophy Society

FSH Watch

FALL 2015

FSH SOCIETY
FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

CONNECTING THE COMMUNITY OF PATIENTS, FAMILIES, CLINICIANS, AND INVESTIGATORS

RESEARCH

Whole-Body MRI Yields New Insights

Another step toward clinical trial readiness

by JUNE KINOSHITA
FSH Society

In 2013-2014, the FSH Society funded a study led by Doris Leung, MD, of the Kennedy Krieger Institute (KKI) in Baltimore, Maryland, which investigated the use of whole-body magnetic resonance imaging (WBMRI) as a method for detecting and characterizing skeletal muscle pathology in facioscapulohumeral muscular dystrophy (FSHD). An imaging method that is sensitive to changing severity in a slowly progressive disorder such as FSHD could not only improve our understanding of the disease and its progression, but also facilitate quicker clinical trials with smaller sample sizes.

FSHD causes slowly progressive muscle weakness that preferentially affects the face, shoulder girdle, and ankle dorsiflexors, and

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From left to right, Rob Dye, Doug Craig, and Gracie arrive in Washington, DC!

ADVOCACY

An Intrepid Scooter Ride Raises Awareness and Funds

Doug and Gracie NYC to DC

by DOUGLAS CRAIG, PhD
Yonkers, New York

The idea that I needed to do something to help raise awareness and research funding for FSHD had been gnawing at me for several years. Last year, I decided it was time to act. I wanted to do something with the potential to introduce FSHD to an audience beyond those with FSHD, their families, and their circle of friends. I also yearned to combine fundraising with something that was a little physically challenging.

I had recently purchased a Pride Victory Sport model scooter to use outdoors, especially for taking Gracie, our Bernese Mountain Dog mix, on long walks. The new scooter was much more comfortable and stable than my smaller indoor model and had a range of about 15 miles with a top speed of 8 mph. I realized that if I was able to increase the range by adding an external lithium battery,

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WHAT'S INSIDE

A Kind of Magic

Dear Friends,
This October we had our first-ever gala in Los Angeles, an incredibly fun Halloween costume ball aptly named "A Ghostly Gala to Vanish FSHD." There, June spoke of the importance of raising public awareness, because you first must make something visible before you can make it vanish. That's just Magic 101.

Dan Perez

June Kinoshita

But it's a serious point. How can we make FSHD more visible? One way is to stir up a cauldron of activity. This issue overflows with reports of our accomplishments. In the annual research review section, we update you on current FSH Society-funded research—projects you are supporting through your gifts. These 18 projects run the gamut of research, from inquiries into fundamental mechanisms to focused searches for drug candidates and development of tools for carrying out clinical trials. Many of these were presented at the Society's annual international research workshop in October; you can read about them in our story on page 6.

In addition, we spotlight three important advances in FSHD research: a first-of-its-kind international study of infantile or early-onset FSHD, a study using magnetic resonance imaging to shed light on FSHD's impact on muscles throughout the body over time, and an ingenious use of gene editing technology to shut down the genetic machinery of FSHD.

While the Society's research portfolio has grown rapidly, we have also worked hard to expand services to individuals and families living with FSHD. A major milestone this year was the American Academy of Neurology's evidence-based FSHD care guideline. The Society was involved with the Centers for Disease Control and AAN in reviewing the guidelines and is taking a leading role in making sure it gets out to patients and healthcare providers. You can download the guideline summaries from our website. We also completely updated our "About FSHD" brochure, which you can request or download from our website or by calling (781) 301-6651.

Our grassroots networks have exploded this year. FSH Society member gatherings around the country have grown fivefold in just one year, and now serve patients and families in 10 locations around the U.S. We are so grateful to the volunteer organizers of these meetings.

The FSH Society has built a powerful capacity to mobilize researchers, patients, and industry. But now we must do much more. It took 24 years to reach this point. We are positioned to have a powerful impact on accelerating research and getting to treatments. But to achieve our common goal, we need your help more than ever to make your voice heard in your community, in Congress, and at the National Institutes of Health, and to activate funding through personal gifts, holiday and birthday letters, and fundraisers large and small. If enough of us stir things up, we will make FSHD visible.

This year we have set an ambitious goal of raising $2,445,000. The FSH Society's Board of Directors has pledged $384,805 toward this goal and challenges you to match this amount. Please consider what the FSH Society means to you and what your future would look like without the FSH Society … and then give as generously as you can—for yourself, for all who live today with FSHD, and for future generations.

With sincere thanks to all our supporters, staff, Board of Directors, and Scientific Advisory Board, we wish you all a wonderful holiday season.

Sincerely,

June Kinoshita
Executive Director, FSH Society

Dan Perez
President & CEO, FSH Society

FSH Watch
FALL 2015

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What FSHD Has Given Me

Learn, let go, and find beauty in new places

by MEREDITH L. HUML
Raleigh, North Carolina

As a muscular dystrophy sufferer—I was diagnosed with FSHD at Duke University's Muscular Dystrophy Association (MDA) Center in 2003—the best advice I could offer someone who is newly diagnosed would be, "Don't hesitate to educate yourself on your affliction." Figuring out what exactly you are dealing with and how you can help yourself and your loved ones will make the situation easier to cope with as a whole.

Connect with advocacy groups and other patients

Fortunately, awareness of muscular dystrophy continues to grow. Scientists continue to produce more findings, and hopefully one day there will be a cure for every type of MD. As our world becomes more connected, it is easier to read up on updates in research, learn the symptoms and causes of your malady, and connect with others through social media.

Patient advocacy is vital in fighting muscular dystrophy, as it is with any medical condition, especially those with limited awareness and no cure at this point in time. There is always the option of making a donation to organizations that fight against MD, setting up a fundraiser for the cause, or working at a summer camp for children afflicted.

Using your voice is an important tool as well. The Muscular Dystrophy Association provides a page on which you can find your elected officials who pass important pieces of legislation affecting muscular dystrophy patients and their families.

Ask for help when you need it

As a patient, I understand that this disease comes with more than just physical side effects. It can be humiliating, frightening, stressful, disheartening, and confusing. I was diagnosed with depression in high school after I began to accept the changes going on in my body and when I began to try to accept and recognize my limitations.

Even without the daily struggle of coping with muscular dystrophy, it can sometimes be difficult and embarrassing to admit our weaknesses and ask for help when we need it. We want to be independent, we want to take care of things ourselves, we want to say, "I did this for myself. I didn't need help."

As the years have passed, I am still learning how to ask for help. I am learning how to undermine my stubbornness, to talk about and admit openly the simple truth that I am physically weaker than most people I encounter. I am learning to offer a compromise when invited to do things I may not have the strength to do, or learn how to tell others I'm going to have to "sit this one out." And I am learning to watch others run and dance and climb with joy instead of resentment, jealousy, and anger.

Try exploring new pastimes

It is easy to feel cheated when you don't have the same opportunities, and it is easy to feel excluded.

I began studying dance when I was three years old. I fell in love with it. It was a way to be active in a fashion that I felt coincided with my very soul. It was a way for me to get stress out. I took tap, ballet, hip-hop, and modern/contemporary classes. Being in a studio was like being at a different kind of home.

When I was forced to take a lower-level dance class as a sophomore in high school, the same one I had taken as a freshman, I was angry. I couldn't physically keep up with the higher-level classes, and it tore at me. I had been a dancer for years and years; I could choreograph a routine in a short amount of time. I knew how to do all the moves and heard counts and beats in every song I heard. I daydreamed routines in my mind and couldn't listen to a song without wanting to move some part of me.

After sophomore year, I admitted defeat to myself. I stopped dance altogether. I canceled my subscription to my dance magazine and shoved my tights and leotards into the bottom of my drawer. To give up something that seems like your life, something that you're passionate about, is torturous. It brings about some of the emotions I previously mentioned.

As someone with muscular dystrophy, you are most likely able to relate. To give up something like that, and on top of that, sometimes even simple daily tasks, is a complete life changer. And seeing others accomplish things you wish to as well is frustrating.

> *"It is okay to hurt, to cry, to feel sad and lazy some days. It will rain some days. Just remember the good weather, and know that it is coming. Don't be afraid to let others help you, and don't be afraid to offer your help to others."*
>
> MEREDITH HUML

Enjoy simple pleasures

There is, however, good news. There is always a silver lining if you look closely enough. You did not choose this. Your loved ones who suffer from muscular dystrophy did not choose this. Blaming yourself, blaming others, and being angry are things that will cripple you even more.

Let any anger you feel serve as motivation for something great, or throw it away. You may be unable to run down the soccer field or climb mountains by yourself. You may have to give up things you find hard to. There are other things you can try, other

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When Muscular Dystrophy Is Personal—And Global

Kenyan patient's journey of a lifetime

by FRED THYS
WBUR, Boston, Massachusetts

Every once in a while, I'm grateful I live in such a medically minded town, with many deep thinkers trying to figure out treatments and cures for some very tough diseases.

I felt this way last summer, at a conference in Boston on facioscapulohumeral muscular dystrophy, a genetic disorder that affects one in 8,333 people and has no treatment or cure. I did not attend the meeting due to some theoretical interest in the topic; for me, it's personal.

My mother and grandmother suffered from the condition, and so does my brother. It causes gradual loss of muscle function, notably in the face and in the muscles that mobilize the shoulder blades and the upper arm, but also in the legs.

At the 2014 FSHD Connect meeting in Boston, from left, Keziah Waithaka, June Kinoshita, and Chris Chege.

My brother first developed symptoms when he was 15 and found that he could no longer run as fast as his high school soccer teammates. Since the age of 43, he has been confined to a wheelchair or scooter, unable to walk or stand.

But at the conference in August of 2014, I also realized that this illness with such a profound impact on my family also has a global reach. Indeed, in regions like Africa, the condition is only just beginning to be acknowledged.

Enter: Chris Chege

I first saw Chege sitting on a tall stool at the back of the room with his wife Keziah. Their presence proved that the condition affects Africans, too—something that isn't widely known. Chege and Keziah had traveled to Boston from their home in Thika, in central Kenya, 30 miles northeast of Nairobi.

An interview with Chege pointed to one possible reason that conference room was full mainly of white people: Most people with the condition in Africa may not have been diagnosed with it yet.

But Chege said he sees others with FSHD in Kenya. He can tell "by the way they walk," he said. "I see them on national television when journalists go to their homes to interview them." The television journalists, Chege said, report that the families he sees on television with the symptoms of FSHD are bewitched. "The way they walk, I can tell that's muscular dystrophy," he said. His own condition was a mystery to him for nearly 20 years.

When he was a teenager, he first realized that he could not keep up with other people. "Back home, my father was a farmer," Chege said. "We used to pick coffee berries from our farm. Once we pick the coffee berries, we have to take them to a processing machine, and you take what you pick."

Chege would have to carry 45 pounds of coffee berries at a time. One day, he found that he was unable to carry so many berries. "I used to receive a lot of beatings from my father and my mother because they thought I was just lazy," he said.

Chege decided on his own to see a doctor, who gave him medication that produced "a lot" of side effects on him, he said.

There are no medications approved anywhere for the treatment of FSHD.

It was not until the year 2000, at the age of 34, that he was diagnosed with muscular dystrophy.

"Life is very harsh having a muscular dystrophy condition, because in my town, it's very hilly, so walking around is quite difficult, and if I have to walk around, I have to have somebody to help me, and you see, almost everybody is busy," he said.

So most of the time, Chege said, he sits at home.

"It's actually very, very harsh in Africa," he said. Chege and his wife have two boys, ages 16 and 10. "The way they behave during their daily activities, she senses they may be affected, also," he said.

Chege found out about the FSH Society's biannual conferences that bring together patients, their families, doctors, and researchers.

Peter Jones was one of the researchers at the conference who met with Chege. Jones is conducting research at the University of Massachusetts Medical School. The genetic sequence that causes FSHD, known as 4q35 D4Z4, is present in healthy people as well as people affected by the disorder. In healthy people, the sequence is suppressed. For some reason, in people affected by FSHD, the suppression mechanism doesn't work. Jones is trying to figure out why.

"I decided to come to this conference in Boston to meet other patients who have the same condition and also to learn more about this condition, and to meet the scientists, the doctors, and to gather more information so that I can be able to educate others back home," Chege said. But the trip to Boston was expensive. He had to sell some of his land in order to travel to the conference.

"Most of my friends, family members, thought I was mad," he said. "To me, knowledge is more than those properties. "He was not able to afford bringing the entire family, so the boys stayed in Kenya.

Chege said that because his wife was able to attend the conference, she has gained understanding into his condition.

"I don't regret disposing some of my properties to come here," he said.

At the conference, he said, researchers offered to test him. He

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Update on Early-Onset FSHD Study

Insights on symptoms, biology, and quality of life

by YI-WEN CHEN, PhD, and JEAN MAH, MD
Washington, DC, and Calgary, Canada

Chen and Mah are investigators for the Cooperative International Neuromuscular Research Group (CINRG) studying early-onset FSHD. The FSH Society co-funded this study with the FSHD Global Research Foundation and Muscular Dystrophy Canada.

While most people with FSHD develop muscle weakness during late teen years or adulthood, about 4 percent of patients have early-onset FSHD. Patients with early-onset FSHD develop disease symptoms early in life (facial weakness before 5 years old and shoulder girdle weakness before 10 years old), have more severe muscle weakness, are more likely to need a wheelchair later in life, and have a higher chance of developing non-muscle symptoms (hearing loss, retinal vascular disease, developmental delays, and cognitive/intellectual disabilities).

FSHD is caused by aberrant expression of double homeobox protein 4 (DUX4) in patients' cells. It is believed that patients with early-onset FSHD have genomic mutations that allow for a higher frequency of DUX4 expression in cells (associated with fewer D4Z4 repeats compared to late-onset patients), which contributes to the earlier and more severe disease symptoms.

In 2010, the FSH Society released a request for application (RFA) to study early-onset FSHD. In response to the RFA, our research team proposed to conduct a multicenter collaborative study on the clinical features, expression profiling, and quality of life of individuals with early-onset facioscapulohumeral muscular dystrophy.

The main goals of the study were to establish a standardized muscle testing protocol in children and young adults with early-onset FSHD, to better understand clinical phenotypes of early-onset FSHD, and to evaluate the impact of the disease on health-related quality of life and disability across different age groups. In addition, optional blood samples were collected for future biomedical research.

The studies were conducted by the Cooperative International Neuromuscular Research Group (CINRG), which was founded in 1999 at Children's National Medical Center and has more than 30 neuromuscular clinical centers currently in the U.S., Canada, and beyond. Eleven CINRG sites participated in this study and had enrolled a total of 53 patients when enrollment was completed in early 2015.

In this study, the median age of participants was 17.9 years at enrollment, with a shorter D4Z4 region (median of 16 kb) as expected for early-onset FSHD. While the data analyses are ongoing, we found that extramuscular features such as retinal disease and cognitive disability are relatively uncommon. One-quarter of the participants had a history of hearing loss, and 20 individuals (38 percent) are dependent on a wheelchair for part-time or full-time assisted ambulation.

Many individuals reported symptoms such as muscle pain and/or fatigue, and their pulmonary functions will need to be followed closely due to initial testing showing lower lung capacity.

Despite their prominent muscle weakness, many individuals compensated well and had a relatively good psychosocial quality of life.

In addition to evaluating clinical presentations, we studied the blood samples collected from participants by using a mass spectrometry-based proteome profiling technique to identify protein biomarkers in peripheral blood samples, which may potentially be used as surrogate markers for evaluation treatment efficacy in future clinical studies.

The research team recently received additional support from the FSHD Global Research Foundation and aTyr Pharma to conduct a longitudinal study with this patient cohort that includes three additional visits (six months apart). This will allow us to study changes over time in manual and quantitative muscle strength and function testing, as well as changes in the clinical phenotypes in children and adults with infantile-onset FSHD. The blood samples collected will allow us to better prioritize potential biomarkers.

"The main goals of the study were to establish a standardized muscle testing protocol in children and young adults with early-onset FSHD, to better understand clinical phenotypes of early-onset FSHD, and to evaluate the impact of the disease on health-related quality of life and disability across different age groups."

Ashleigh, age 12, was diagnosed when she was three.

This study would not be possible without the initial support from the FSH Society, followed by support from Muscular Dystrophy Canada and the FSHD Global Research Foundation. The international collaborative effort made it possible to identify and recruit participants all over the world.

Last and most importantly, this study would not be possible without the support from all the participants and their family members.

The valuable clinical and biological data generated from this study will greatly increase our understanding of early-onset FSHD. A well-characterized patient cohort is also an ideal population for future clinical trials. FSH Watch

2015 Annual International Research Workshop

Progress and continuing challenges in FSHD research

by CHARIS HIMEDA, PhD
Worcester, Massachusetts

Charis Himeda is a Research Associate II in the lab of Peter Jones at the University of Massachusetts Medical School.

The FSH Society's 2015 International Research Consortium and Research Planning meetings, held in Boston on October 5-6, 2015, brought together over 100 investigators, including leaders in FSHD research and many industry sponsors, to discuss advances made over the past year. In a striking change from previous years, the majority of research presented was translational.

The shift in focus to therapeutic development serves as an encouraging reminder that, in work by Richard Lemmers, PhD; Stephen Tapscott, MD PhD; Silvère van der Maarel, PhD; and their collaborators, the fundamental genetic lesions causing both forms of FSHD have been identified and characterized. This seminal accomplishment has paved the way for a multitude of new studies aimed at understanding the downstream pathways that lead to disease.

But dissecting these pathways is not a simple or straightforward endeavor. Whereas congenital myopathies and other muscular dystrophies display strong phenotypes (observable characteristics), FSHD exhibits a bewildering lack of detectable pathology during the early stages. This continues to be a major hurdle in understanding and overcoming the disease.

The current best model in the field proposes that genetic and epigenetic alterations in an FSHD individual lead to bursts of aberrant DUX4 protein expression in rare muscle cells, which cause accumulated pathology over time. Consistent with this model, when DUX4 is forcibly expressed, it is highly toxic to both cultured cells and animals. However, when cells are taken from FSHD patients and grown in the lab, they display more subtle (and inconsistent) defects, and early-stage FSHD biopsies reveal generally healthy-looking muscle.

Existing DUX4 mouse models have been problematic. These mice either die prematurely or, in contrast, show no ill effects in muscle. These limitations have spurred efforts to achieve an FSHD-like phenotype by other means. The labs of Joel Chamberlain, PhD, and Scott Harper, PhD, are using viruses to deliver DUX4 into mice or monkeys. The lab of Kathryn Wagner, MD PhD, of the Kennedy Krieger Institute in Baltimore, Maryland, is xenografting human FSHD muscle into the hindlimbs of mice.

While many models of the disease are being employed, each comes with its own set of advantages and limitations. Primary FSHD muscle cells contain a patient's own genetic signature, but they can only be propagated in a culture dish, away from the physiological signals these cells would normally see inside the patient. Grafting a patient's muscle into mice restores the environment of a living animal but in the absence of normal immune signals, because these mice have suppressed immune systems in order to prevent the grafted muscle from being rejected. Finally, studies in which DUX4 is forcibly overexpressed either in vitro or in vivo suffer from questionable relevance to real disease mechanisms.

Many strategies are being used to reduce DUX4 expression,

FSHD researchers engaged in animated discussions during breaks. Co-chair Stephen Tapscott, PhD, (above, lower left) challenged the attendees to define top research priorities for the coming year.

with the goal of eventual testing in clinical trials. These include antisense oligonucleotides and microRNAs (work from the labs of Julie Dumonceaux, PhD; Charles Emerson, PhD; and Scott Harper, PhD), as well as inhibitory compounds (Michael Kyba, PhD, and Fran Sverdrup, PhD).

Other studies are aimed at dissecting the DUX4 protein and its interaction networks (work from the labs of Alexandra Belayew, PhD; Scott Harper, PhD; Lou Kunkel, PhD; Jeff Miller, PhD; and Peter Zammit, PhD). DUX4 has specific effects on global gene expression, both at the mRNA level and, in new work from Stephen Tapscott and Robert Bradley, PhD, at the protein level.

Chad Heatwole, MD; Jeffrey Statland, MD; and their collaborators are making improvements in the outcome measures needed to gauge the efficacy of therapeutic candidates, once such candidates are ready for trials.

Whether DUX4 is expressed in muscle satellite cells—the stem cells required for muscle regeneration—is still an open question. If DUX4 interferes with the ability of satellite cells to self-renew or give rise to new muscle, this might provide a partial explanation for the generally late onset of FSHD—and might require an effective treatment to target these cells.

Meanwhile, genome editing for FSHD and other diseases is in the early stages of development, as proof-of-principle studies continue to refine a very powerful potential avenue of therapy.

Although progress is being made, we are still left with the question, What is the dominant pathological mechanism in FSHD? If the answer is that there is no single dominant mechanism, only a host of things that can go awry downstream of the genetic lesion, this is a strong indication for therapies targeted upstream, rather than downstream, of DUX4 expression. FSH Watch

Editor's note: The FSH Society's international research workshop has been held annually for the past 19 years. We thank this year's co-chairs: David Housman, PhD, of the Massachusetts Institute of Technology and chair of the FSH Society Scientific Advisory Board; Michael Altherr, PhD, of Los Alamos National Laboratory and a member of the FSH Society Scientific Advisory Board; Stephen Tapscott, PhD, of the Fred Hutchinson Cancer Institute; and Silvère van der Maarel, PhD, of Leiden University. Daniel Perez, President & CEO of the FSH Society, served as organizational chair. We also thank the meeting sponsors: Acceleron; Association Française contre les Myopathies (AFM); aTyr Pharma; BioMarin Pharmaceutical; Facio-Therapies; FSHD Canada; FSH Society; FSHD Global Research Foundation; Genomic Vision; Genzyme, a Sanofi Company; Idera Pharma; Muscular Dystrophy Association United States; Muscular Dystrophy Campaign United Kingdom; NIH Eunice Kennedy Shriver NICHD Senator Paul D. Wellstone MDCRC for FSHD at University of Massachusetts Medical School; Regeneron Pharmaceuticals; and Sarepta. The program and abstracts book are available online at *https://www.fshsociety.org/international-research-consortium/*.

Any Body Can Dance!

DOING RUMBAS FOR RESEARCH

On September 4, 2015, the Fred Astaire Dance Studio of Brandon hosted the first ballroom dance fundraiser in Florida called "Any Body Can Dance!" (ABCD). Kelle and David Chancellor, owners of the Fred Astaire Dance Studio of Brandon, Florida, offered to host an event to help bring awareness of FSHD to the community after reading a post I wrote on Facebook earlier this year.

The fun started with planning the event, dances, getting donations, etc. We started out slow, but then everything fell into place, the pledges were coming in, and the excitement was building. The evening came, and everyone got dressed up and arrived at the studio ready to show off their dance moves.

The evening started with a meet and greet, followed by food and beverages. Kelle Chancellor introduced my primary care physician, Dheeraj Reddy, MD, from Valrico Brandon Medical Center. He spoke at the start of the dance event on the different types of muscular dystrophy, focusing on FSHD. He talked about the genetics, symptoms, and possible treatments. There were two TVs showing videos from the FSH Society website to educate the audience on FSHD.

The evening was filled with supporters and donors showing off their dancing skills from different dance styles, such as the waltz, rumba, and swing. There were also salsa group classes for everyone. We had spotlights on Argentine tango and rumba along with 66 dances from sponsors.

ABCD was a great success, due to the support of the Fred Astaire Dance Studio of Brandon, and of family and friends from New York, New Jersey, Connecticut, Texas, California, Iowa, Minnesota, and Florida. We raised a total of $7,563 for the FSH Society's research to help find a cure!

I would like to thank June Kinoshita and Chandra Budhram for their help. Thank you to the Brandon FADS for hosting a spectacular event! My heartfelt thanks to Kelle and David Chancellor, Austyn, and Jose for being extraordinary instructors.

I believe that what makes teachers amazing is when they can adapt to students' abilities, or lack thereof, and still impart their knowledge to the student. Kelle is a great instructor, and I am thankful to be her student.

I would also like to thank my fellow classmates for their support. It is my honor to dance with them. People walked into the Brandon Fred Astaire Dance Studio and danced out more knowledgeable about the disease. It was a night to remember, and we raised more money than my intended goal, which made it even better.

–Bobby Budhram, Valrico, Florida

Bobby Budhram (at left) gets into the swing of things at the Any Body Can Dance fundraiser.

New Manual on Muscular Dystrophy Spotlights FSHD

Profits are being donated to the FSH Society

ADAPTED FROM QUINTILES' INTRANET NEWSLETTER

Raymond Huml, DVM RAC

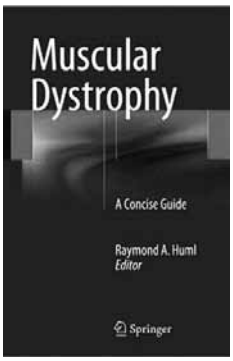
Raymond A. Huml, DVM RAC, has led the development of a new book on muscular dystrophy that provides clinicians, researchers, pharmaceutical executives, and patient advocacy groups an easy-to-read and comprehensive resource on this rare disease.

Titled *Muscular Dystrophy: A Concise Guide,* the 15-chapter book provides extensive background information on the nine major types of muscular dystrophy (MD), including underlying genetic and molecular mechanisms, current treatments, physical therapy and orthotic devices, orthopedic management, the global regulatory landscape, and challenges in obtaining approval for therapies. The book also examines the activities of patient advocacy groups and offers an update on patient registries.

While Huml, head of Global Biosimilars Strategic Planning in the Quintiles Biosimilars Center of Excellence, wrote or co-wrote eight chapters of the book himself, he collaborated with other physicians within the industry and academia to lend their unique perspectives on MD for the book.

"Many factors make this the right time for a concise book on muscular dystrophy," said Huml. "First, there is a high, unmet medical need for MD treatments. Second, breakthroughs in science, technology, and gene manipulation are identifying new targets. The biopharma industry continues to look for ways to decrease risk while investing in products for the treatment of MD, and recent regulatory advances will be helpful."

The book focuses particularly on the most prevalent type of MD, called facioscapulohumeral MD (FSHD), and the most severe, Duchenne MD (DMD). Becker MD (BMD), which is mechanistically related to DMD, is another form of MD discussed in the book.



In his foreword to the book, Ross M. Tonkens, MD, of the Science & Technology Accelerator Division of the American Heart Association describes Huml as "the perfect person" to assemble the distinguished group of authors for the book.

"Perhaps most pertinent is the fact that Ray and his wife Leslie are the parents of two children, both of whom suffer from [FSH] muscular dystrophy," Tonkens wrote.

Huml was quick to point out that as a company, Quintiles is doing its part for muscular dystrophy research, including implementing the Muscular Dystrophy Association's U.S. Neuromuscular Disease Registry.

"The great work Quintiles and others within the industry are doing for MD makes me hopeful that there will be a cure in the not-so-distant future," said Huml. FSHWatch

Bob Smith and the Cape Cod Walk 'n' Roll for FSH Muscular Dystrophy

HIS PASSION TO HELP WAS AN INSPIRATION TO MANY

Bob Smith passed away earlier this year from respiratory complications associated with FSHD. He contributed much through his service on the FSH Society's Board of Directors, his work as a lawyer on Cape Cod, and his efforts to protect conservation land in his town of Harwich. (See *FSH Watch* Spring/Summer 2015 issue for Bob's obituary notice.)

But I knew Bob as the co-chairman of the fundraising and public education event we organized: the Cape Cod Walk 'n' Roll for FSH Muscular Dystrophy, a name Bob chose. He reached out to his wide circle of friends and brought in thousands of dollars of donations for each of the five years that the event ran. The event was a bit of inspiration for other patients to create fundraisers of various types and sizes. There were few others when it began in 2008, according to Nancy Van Zant, former FSH Society executive director.

"He did not hesitate to ask friends, family, and colleagues on the Cape to support research in the disease, and they responded generously. His friends were there for him," Nancy said. "Respect for him was apparent all around. I appreciated the opportunity to work with him."

In addition to raising money and awareness, the event brought FSHD families and friends together, starting with Bob and me: We were the first Cape people each of us had met that had FSHD.

"He was so down-to-earth, so funny, and so good," recalled Maureen Hourihan, who met Bob several years ago through real estate dealings. She and her husband Paul became friends with Bob and his wife Patti, and had dinner with them a few weeks before he died.

Maureen volunteered to help with the walk at Bob's request. "It was so personal and so fun. We were so happy to come and participate," she said. "Finally, we could do a favor back to Bob."

Bob may have been hampered physically, but it didn't stop him from working hard or enjoying life, right up to the end. I remember his fondness for good wine and the way he delivered zingers in a deadpan manner followed by a devilish smile. His humor, intelligence, determination, and generosity brightened the lives of those he met. I miss him and wish I'd gotten to know him better.

–Rich Holmes, Hyannis, Massachusetts

Gene Interference Technology Used Against FSHD

Proof-of-principle study is the first to use CRISPR technology on the "repeat genome"

by JUNE KINOSHITA

A research team led by Peter Jones, PhD, at the University of Massachusetts Medical School (UMMS) has successfully used a derivation of the CRISPR-based gene-editing method known as dCas9 to target and silence the DNA sequence implicated in FSHD.

The work represents two firsts. "While CRISPR technology has been used successfully in early studies of genome editing, this is the first report in which a CRISPR-based system has been used to ameliorate pathogenic gene expression in FSHD," wrote the paper's lead author Charis Himeda, PhD. "This is also, to our knowledge, the first time the technique has been used successfully in primary human muscle cells."

The CRISPR-Cas9 system originated from the discovery of a mechanism that bacteria employ to purge their genomes of foreign genes, somewhat like a primal immune system. Molecular biologists have figured out how to harness this natural system to specifically target genomic sequences.

Typically, the CRISPR-Cas9 technology is used to cut the DNA to change or remove specific sequences. However, the potential off-target effects of introducing non-specific cuts to the genome are a serious concern.

Study co-authors Takako Jones, PhD, Peter Jones, PhD, and Charis Himeda, PhD

As an alternative, the CRISPR-dCas9 system does not cut the DNA, instead altering the expression status of the targeted gene by recruiting either gene activation or repression proteins. In theory, CRISPR-Cas9 could be used to treat classic genetic disorders by editing gene sequences, while CRISPR-dCas9 could be used to silence mutant disease-causing genes or activate beneficial genes.

In FSHD, muscle degeneration results not from a misspelled gene but rather from a different type of genetic error. The most common form of the condition, FSHD1, is caused by a shortening of a variable tandem repeat region of so-called "junk" DNA on chromosome 4. This repeat genome region consists of numerous repetitive units called "D4Z4." Normally, humans have between 11 to over 100 D4Z4 units in this location, but in individuals with FSHD1, there are only between one and 10 units.

This repeat region harbors a gene called DUX4. Normally, this gene is repressed. But in FSHD, the reduced number of repeats, together with loss of methyl groups in the region, causes changes in the structure of the chromatin (the complex of molecules that form the chromosome). The result is that DUX4, and possibly a number of noncoding RNAs, becomes prone to being expressed, triggering chemical events that lead to muscle destruction.

Several research groups, including ones funded by FSH Society grants, are using CRISPR-Cas9 to edit the DUX4 gene in an effort to render it non-functional. The UMMS group, however, decided to more broadly target several regions of the D4Z4 repeats. "The D4Z4 repeats encode multiple coding and noncoding RNAs, which have the potential to play downstream pathogenic roles in FSHD. Thus, targeting the FSHD locus to return the chromatin to its non-pathogenic, more repressed state might be more therapeutically beneficial than simply targeting DUX4," the authors explained. The methods developed and demonstrated by this study "should pave the way for more effective and stable correction of FSHD and other epigenetic diseases."

The work may have powerful implications beyond the relatively rare incidence of FSHD. "With increasing evidence that the repeat genome (comprising nearly half the human genome) plays important roles in gene regulation, additional diseases will likely be found associated with aberrant repetitive genomic sequences," the authors said. "We have provided the first evidence that the repeat genome can be targeted via the CRISPR system, which is likely to prove useful as this hitherto overlooked portion of the genome is decoded."

The newly published work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases grant #1R01AR062587 and the Association Française contre les Myopathies grant #AFM15700. The FSH Society funded work in the Jones lab that laid the foundations for the current study and supported development of the UMMS Wellstone Center FSHD cell and DNA repository used in this research.

Bob Smith (right) thanks supporters at the Cape Cod Walk 'n' Roll in 2014.

Reference

Charis L. Himeda, Takako I. Jones, and Peter L. Jones. CRISPR/dCas9-mediated transcriptional inhibition ameliorates the epigenetic dysregulation at D4Z4 and represses DUX4-fl in FSH muscular dystrophy. Molecular Therapy, accepted article preview online 03 November 2015; doi:10.1038/mt.2015.200.

Designing an Accessible Kitchen

Safe, reachable, warm, and inviting

by MARGE BRCHAN
Blaine, Minnesota

Cooking is something I love to do. So when I found that my FSHD symptoms had reached a point where I couldn't cook safely without the help of my husband Dale, I decided it was time for a kitchen makeover.

At first, I thought this would require just a few tweaks, but I eventually realized I'd need to gut our old kitchen and redesign from the ground up. It was a big investment, but worth it for our long-term health. Being able to do home cooking and entertain family and friends ensures that I'm getting good nutrition and exercise. A well-designed kitchen would allow me to combine all of the components of positive living and a good quality of life.

I enlisted the help of Susan E. Brown Interior Design in St. Paul, Minnesota. My topmost concerns were safety and functionality. I can lose muscle strength quite suddenly, which is dangerous if I'm lifting a hot, heavy pan out of the oven. So Susan designed the wall oven to be at countertop height, with locking oven shelves.

The large island is a key component of the kitchen. It is designed to provide two levels for cooking. It includes a drawer microwave and a seating area for work. The "reachable" spaces all ensure accessibility and my safety.

One of the easiest changes was to bring the upper cabinet above the dishwasher area down to the countertop for ease of putting clean dishes away. This function was aided by the change of a standard door style dishwasher to two pullout dishwasher drawers. Both of these items could easily be changed in an existing kitchen for better function without a major kitchen remodel.

Susan also designed rollout and pulldown inserts in drawers and cabinets so that I could reach their contents more easily. She designed plenty of storage space at heights I could reach—the top drawers in the lower cabinets and the lower shelves of the upper cabinets—so now I have more accessible storage than I had before.

I use a walker now, and may someday require a scooter or wheelchair, so the kitchen area needs to be free of barriers. The floors have to be walker-friendly and forgiving if I were to fall. It couldn't be slippery or too tacky. We found a faux wood laminate that did the trick.

Another major safety item is the induction cooktop. I had wanted gas

Goals for kitchen redesign

1. An accessible kitchen that worked for me but did not look institutional as most "accessibility designs" tend toward.
2. Colors and materials that would meet Dale's and my different color preferences. (Not an easy goal to achieve!)
3. A wall oven that was level with the counter so that I could place things in the oven, work with them while they were in the oven, and remove them when they were hot. Safety was a major concern due to limitations in my balance and ability to lift anything with weight.
4. Same was true for the microwave, which was originally above the stove.
5. Cupboards/cabinets that would provide accessible storage space.
6. A space designed so I had separate areas for baking, cooking, and cleanup that did not require reaching down and in or up for heavy items.
7. The design needed to allow me to be able to slide pans or bowls along the countertop with resting points for heavy objects.
8. An efficient work space requiring fewer steps and with counter areas I could use for different purposes: Dale's prep area for his salads, mine for prep tasks, one for baking, one for snacks, etc.
9. Work space for my hobbies at a height I could use—not the bar height that was in the original kitchen.
10. All space to be usable if I needed to use my walker or in the future if I need wheeled mobility.
11. Counters at two levels so I could use the normal level for working in a standing position and a lower counter where I could do food prep in a sitting position.
12. A floor that was not too tacky or too slippery.
13. A design that others would like and would enhance the value of the house for future sale, and not be labeled a "house for the handicapped."

(better for cooking), but because of arm weakness coupled with a flame, I was convinced to use induction. Long story short—I love it! And, after saying for years if I ever did a kitchen redo I would not settle for anything less than gas, I have become an ardent fan of induction stovetops. Not only are they safe, but they are also a great tool for cooking.

Susan even figured out how to combine Dale's and my own very different tastes in color. I like primary colors, while he prefers muted shades. Susan took it as a creative opportunity. The middle island is painted deep blue (my favorite color), while the walls are sage green (for Dale). Both go well with the maple cabinets and countertop, Crema Bordeaux, a combination of rich gold, burgundy, and charcoal. The random glass tile backsplash design of greyed blue, burgundy, and sage green simultaneously tie in the colors of the countertop.

I wanted my kitchen to be warm and inviting. Everything is workable for me, and very handy. There's no space in my kitchen I can't reach. I can cook without having to call Dale to help. He loves it. He was tired of hearing me ask, "Can you help me with this?" And everybody loves the way it looks. People would not know it's accessible. FSHWatch

Project and product information:

Designer: Susan E. Brown Interior Design
www.susanebrown.com
Phone (651) 330-8707

Contractor: Greg Giddings, Giddings Construction
Phone (763) 413-9919

PRODUCTS:

OVEN	KitchenAid Built-In Single Self-Clean 30" Model
STOVE TOP	KitchenAid Touch-Activated Electronic Induction Cooktop
STOVE TOP VENT	KitchenAid Range Hood
DISHWASHER	Fischer & Paykel DishDrawer: Tall Height Double Model Classic
MICROWAVE	Sharp Microwave Drawer
SINK	Blanco Diamond 1¾ Sink: Color—Cinder
FAUCET	Moen Arbor With Motionsense
FLOORING	Mannington Revolutions
GARBAGE CONTAINER	Lee Valley Hardware Catalog *(www.leevalley.com)*

Special features that achieved my goals

1. Wall oven—shelves lock and middle rack aligns just above counter height.
2. Induction stovetop works as well as gas, if not better, and has no heat or flame. (I can't say enough about how much I love this appliance.)
3. Two-level island with built-in drawer microwave that opens and closes with touch.
4. Island also has a pullout cutting board to help with transfer for heavy items in and out of the refrigerator.
5. The island's lower area is also used for casual eating.
6. Kitchen faucet has touchless on and off options.
7. Dishwasher operates like a drawer, requiring no bending or reaching.
8. Counter-level cupboard above dishwasher so dishes may be easily transferred.
9. Many accessible drawers throughout the kitchen including the island.
10. A lower cupboard with pullout shelves.
11. A pullout drawer with slots for trays and large baking pans.
12. Pulldown spice racks.
13. Pullout trash can with two bins—one for regular and one for recycle materials.
14. Pantry cupboard with pullout shelves.
15. Laminate flooring. (This item took the longest to find to assure safety.)
16. A table/work area connecting the dining area to the kitchen to use for hobbies/eating/computer work.

NETWORKING

The First Oregon FSHD Meet and Greet

Monthly meetings planned

by TRISHA LYNN SPRAYBERRY
Aloha, Oregon

The first FSHD meet and greet for folks in Oregon was held on August 29, 2015. It was not only the first gathering for people diagnosed specifically with FSH muscular dystrophy in our area, but this meet and greet was special because it was also the very first time almost every person in attendance, 16 in all, had ever met another person, who wasn't a relative, who also has FSHD. Ever.

It was amazing, packed full with great people, great conversations, and was quite informative. It was casual and began with the typical pleasantries.

We shared our experiences with having FSHD, discussed adaptive devices, giving personal comparative observations about what was and was not so helpful in therapies and other treatments for overcoming the challenges of having FSHD, and the need for more support toward research for a cure.

Our first meet and greet reminded us all that we are not alone with FSHD, and support was created for folks here in Oregon.

If you or someone you love is diagnosed with FSHD in Oregon and you are looking for a great experience with others who happen to share a diagnosis, come on out to one of our monthly meet and greets. You just might end up making a new friend or two! FSHWatch

DATES FOR OREGON FSHD MEET AND GREETS

3-5 p.m. • Izzy's
11900 SW Broadway St.
Beaverton OR 97005

December 19, 2015
January 16, 2016
February 20, 2016
March 19, 2016
April 16, 2016
May 21, 2016
June 18, 2016
July 16, 2016

ADVOCACY

Jewelry for FSHD Awareness

Driven by hope

by TRISHA LYNN SPRAYBERRY
Aloha, Oregon

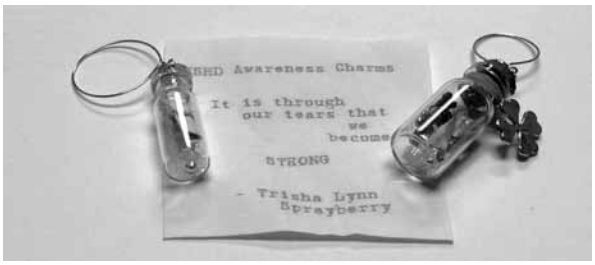
I knew all my life that I have FSHD. It's what my mom, her three siblings, and her mother had. As I grew up, we learned that both of my siblings, my nephew, and my daughter have it, too.

I've watched as my loved ones' disease progressed and they lost their abilities. Walking became stumbling and eventually impossible as they adapted to using a power chair. Three have passed away.

This is what fuels my passion as an advocate and FSHD ambassador to spread awareness for this terrible disease.

One way I try to raise awareness is by making jewelry with a lime green theme, the awareness color for muscular dystrophy. Earrings, necklaces, ribbons, and charms. Earlier this year I created a Message in a Bottle charm. It contains within it this message: "It is through our tears that we become STRONG." I sell them on eBay, and a portion of the proceeds goes to the FSH Society.

When I made these charms, I thought of my family and my hopes for my daughter to be cured. FSHWatch



Trisha's FSHD charms

Stellar Pair Dazzle San Francisco Audience

"SONGS IN THE KEY OF STEVEN BLIER"

The FSH Society's Second Annual "Songs in the Key of Steven Blier," held on Friday evening, July 17, was a grand and elegant affair. Over 150 guests gathered at the Marines' Memorial Club in the heart of San Francisco to bid on a tantalizing array of auction items, enjoy a delectable buffet dinner, and laugh at the antics of auctioneer Liam Mayclem.

The evening was capped by an unforgettable concert. Pianist Steven Blier and soprano Julia Bullock were a pure delight from beginning to end, transporting the audience on a journey across the hills and valleys of experience. We who were in the room were very privileged to be in their presence. The audience hung on every note and erupted in a prolonged standing ovation at the end.

The evening raised over $128,000. Heartfelt thanks to our amazing event committee co-chairs Karen Jewell and Joyce Hakansson, committee members, and dozens of volunteers whose commitment and hard work made the evening possible. We are so grateful to our sponsors and attendees for their generosity.

Steven Blier and Julia Bullock perform at the FSH Society's San Francisco 2015 benefit concert.

ADVOCACY

Laying Tracks for a Cure

Delta Railroad family spearheads 5K and 10K run

by LINDA LAURELLO-BAMBARGER
Jefferson, Ohio

Linda Laurello-Bambarger

Our family has deep roots in Ashtabula, Ohio. In 1957, my great-grandfather started Delta Railroad Construction; as he advanced the company, my grandfather Cosie and grandmother Ida returned to the area to help run the company and build Delta Railroad into what it is today. My dad and uncles grew up here, as did my generation. My sister, cousin Michael, and I now work for the Delta Railroad Construction, too.

Even though our family has been here for years, many people do not know that we have been affected by facioscapulohumeral muscular dystrophy, or FSHD. My Papa Cosie had it. This disease needs to be better understood, and better funded. That is why our family decided to organize a 10K run and one-mile fun run/walk to raise funds for the FSH Society.

We held the first run in October of 2014, and this October we added a 5K run to encourage more people to participate.

My Papa served on the Board of Directors of the FSH Society. He wanted to find a cure, if not for himself, then for his son Paul, who inherited the disease, and for many other family members who are affected.

I think I realized something was wrong when I was maybe three or four. My grandparents took me to a restaurant, and my Papa was having a hard time standing up. I told him, "You can do it, Papa." I knew even at that young age that something was wrong. He got weaker over time until he was in a scooter full time.

FSHD never took my Papa's mind away. He still lived a full life. A lot of people used to go to him for help. He was an engineer and known in the area as the person to go to for any problem with engineering or life. He never turned anyone away. But people knew they had to go to him because he could not venture out to where they were.

My uncle Paul is just like my grandfather. He doesn't let his disease control him. He still goes to amusement parks with his two daughters and enjoys all the rides, especially roller coasters.

This is not to say things are always fine. Like my Papa, Paul has to think constantly about where he is going, how he is going to get in, whether there are steps, if they should not go somewhere, or if the ground is going to be too slippery to get safely into their car. People with FSHD can fall and get hurt easily. If they break a leg, they may never walk again.

There are hundreds of things people with FSHD have to think about just to get through each day. Even things that seem inconsequential have a deep emotional impact. This is why our family wants to find a cure for this disease.

Last year, I joined the Board of Directors of the FSH Society. I wanted to follow in my Papa's footsteps. He was a big proponent of the FSH Society. When he passed away, I felt it was part of my life's journey to help with something he helped to get started. FSHWatch

Linda Laurello-Bambarger is chief financial officer of Delta Railroad Construction, Inc. She lives in Jefferson, Ohio, with her husband and daughter. She serves on the Board of Directors of the FSH Society, a national nonprofit organization combating FSH muscular dystrophy.

NETWORKING

Western Washington

The mini FiSH school

by NANCY PAYTON
Puyallup, Washington

The Greater Seattle area has had a monthly FSHD support group for the past two years in Renton, Washington. This grassroots group is focused on support, education, and advocacy for others. We recently restructured, and on the fourth Saturday of each month there is now a "mini FiSH school" where specific topics are discussed.

At our August meeting, Bob Louden shared an ADA overview and how we can all help businesses improve compliance to increase accessibility for all. This was a hot topic! From sharing war stories to success stories, we learned how we can all do our part.

We are fortunate to have University of Washington researcher Amanda Rickard as a group member, and she brought a new member of her lab to the meeting as well. The Seattle chapter of the Muscular Dystrophy Association is involved and in attendance as well at most meetings.

Six people attended the August meeting, and we were surprised with a newcomer from Richland (halfway across the state)! The regular members want to keep it as a monthly group. We hope that having meetings on Saturdays will increase attendance.

For our September 26 meeting, our mini FiSH school focused on the emotional aspects of FSHD and how we can support one another as symptoms progress. By having an agenda with specific discussion topics, we hope to spur others to want to attend. FSHWatch

ANNUAL RESEARCH REPORT

BASIC SCIENCE AWARDS

Much about the disease process remains shrouded in mystery

by JUNE KINOSHITA and DANIEL PAUL PEREZ

While the DUX4 gene has been identified as a key player in causing FSHD, many essential aspects of the disease process continue to baffle scientists. Does DUX4 play a role during gestation, setting up muscles to be vulnerable later in life? What exactly triggers muscle degeneration? How do muscle cells weaken and die? Are similar or different processes involved in hearing loss and Coats' disease?

We might get lucky and cure FSHD simply by knocking down DUX4 (not that there's anything simple about doing this successfully). But we cannot trust luck. Having detailed, fundamental knowledge of the disease process will expand the possibilities for developing effective and safe treatments.

ROLE OF POLYCOMB GROUP PROTEINS IN FACIOSCAPULOHUMERAL DYSTROPHY

Principal Investigators: Valentina Casà, PhD, and Davide Gabellini, PhD, Division of Regenerative Medicine, Fondazione Centro San Raffaele, Milan, Italy

$45,000 over 18 months

What is driving the changes at the FSHD region?

By Valentina Casà, PhD

Valentina Casà, PhD

In Davide Gabellini's group at San Raffaele Scientific Institute in Milan, my goal is to understand how the region of DNA responsible for FSHD is regulated in healthy and pathologic conditions.

Characterizing the changes that take place as soon as the DNA mutation occurs would give us an important perspective for FSHD research. I am particularly interested in how the deletion of D4Z4 repeats to fewer than 10 (FSHD patients have between one and 10 repeats) could directly promote the alterations in gene expression that have been widely observed. In other words, could this be a mechanism that generates the deleterious molecular downstream effects ultimately leading to the progression of the disease?

In particular, I have been investigating the role of important factors, called Polycomb, which are mediators of gene repression in the region responsible for FSHD. My work suggests that only multiple copies of D4Z4 sequences are able to sustain proper gene repression and that Polycomb is needed for this activity.

My results could explain why patients who carry only a few copies of D4Z4 repeats tend to have a more rapid progression of the disease. In principle, my work could also be useful to think about new therapeutic approaches addressing the regulation of the whole FSHD region.

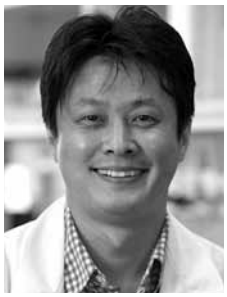
DETAILED TRANSCRIPTIONAL ANALYSIS OF STAGE-SPECIFIC EARLY FSHD MYOGENESIS

Principal Investigator: Gabsang Lee, PhD DVM, Johns Hopkins University School of Medicine, Baltimore, Maryland

$70,977 for one year (FSH Society Max Weintraub Memorial Research Fellowship)

A model for studying FSHD muscle development in early life

By Gabsang Lee, PhD DVM



Gabsang Lee, PhD DVM

The successful isolation of human induced pluripotent stem cells (hiPSCs) offers unprecedented opportunities for regenerative medicine. The hiPSCs do not use any embryonic cells or tissues, but rather are generated from skin cells of each individual. These cells can give rise to virtually any type of cell in our body.

Our lab has developed a straightforward way to direct the hiPSCs to turn into muscle cells, which allows us to generate FSHD patient muscle cells. As the FSHD field suspects that muscle development early in life is responsible for the disease pathogenesis, the muscle cells derived from FSHD-specific hiPSCs will be a useful tool for us to have a better understanding of FSHD.

We are working on isolating very early-stage muscle cells from FSHD hiPSCs. Soon, we hope this humanized cellular model will give us greater insight into the disease process.

Currently, the FSHD hiPSC lines are available to the scientific community for research purposes after an appropriate material transfer agreement (MTA). Please contact Gabsang Lee at *glee48@jhmi.edu*, and the Johns Hopkins Stem Cell Core for further information at *SCCF@jhmi.edu*. Additional muscle cells of the FSHD hiPSCs or the protocol for generating them should be available in the near future.

IDENTIFICATION OF THE UNDERLYING GENETIC DEFECT IN A FAMILY WITH FSHD-LIKE AND OPTIC ATROPHY PHENOTYPE

Principal Investigators: Lionel Van Maldergem, MD PhD, Université de Franche-Comté, Besançon, France, and Björn Fischer-Zirnsak, PhD, Charité-Universitaetsmedizin, Berlin, Germany

$8,000 for one year

Tracking down a gene causing an FSHD-like condition

By Lionel Van Maldergem, MD PhD

The basis of our project is a family with an FSHD-like phenotype showing a combination of progressive muscular disease, optic atrophy, and a metabolic phenotype. In this particular family, whole exome sequencing of their DNA did not reveal any mutations in genes known to cause similar conditions. Nonetheless, we found one gene within the linkage interval to be misexpressed in cultured cells derived from patients.

To identify the supposed regulatory mutation, we performed whole genome sequencing of the affected individuals, with funding from the FSH Society. The sequencing results were recently obtained, and currently the data are being processed.

By using different in silico approaches established at our institute, we can identify various forms of mutations such as alterations affecting protein coding, non-coding regulatory sequences, and structural variants. After we identify the causative mutation, in vitro and in vivo experiments will be performed, depending on the nature of the DNA mutation, in order to further investigate the pathomechanism of this intriguing condition.

The observed combination of FSHD and optic atrophy together with a pronounced metabolic phenotype is, to our knowledge, a unique combination. The identification of the causative mutation thus helps us gain novel knowledge on the regulation and function of a chromosomal region hitherto not linked to a particular disorder. This might also have an impact on the understanding of the FSHD pathomechanism.

Finally, and most importantly, this will provide the family with a molecular diagnosis and knowledge about the nature of their disease after many years of uncertainty.

▶ **DECIPHERING THE CONTRIBUTION OF FAT1-DEPENDENT PHENOTYPES TO FSHD SYMPTOMS AND RELEVANCE FOR THERAPEUTIC DESIGN**

Principal Investigator: Françoise Helmbacher, PhD, IBDM, CNRS UMR 7288, Marseille, France

$138,803 for two years

Probing the FAT1 gene's role in FSHD-like symptoms

By Françoise Helmbacher, PhD

Our laboratory studies neuromuscular development and pathologies in mice and explores novel molecular aspects that contribute to FSHD pathogenesis.

We recently identified the FAT1 cadherin gene, located near the region altered in FSHD, as a key player of muscular biology and as a novel modifier gene in FSHD. Mice without the Fat1 gene exhibit abnormally shaped muscles in the face and shoulder, leading to FSHD-like muscle and non-muscle symptoms. This led us to ask if FAT1 alterations could be involved in contributing to FSHD pathogenesis.

Our lab, together with the Bartoli/Levy and Dumonceaux labs, has found that there is less FAT1 protein in muscles of FSHD1 and FSHD2 patients. We have identified mutations in the FAT1 gene in FSHD-like patients not carrying the classical DNA changes characteristic of FSHD1 or FSHD2.

Our lab uses mouse models to model FAT1-related FSHD-like symptoms and understand how they contribute to FSHD pathogenesis. In particular, we can disrupt the gene in a tissue of choice without altering it in other tissues. We have created mice lacking Fat1 in either muscle or mesenchyme. Both types of mice exhibit reduced muscle strength and FSHD-like phenotypes when adult.

Part of this work was carried out with the support of the FSH Society. With renewed support from the FSH Society, we are now asking whether changes in Fat1, which can lead to these FSHD-like symptoms, can be caused by or in addition to the excessive production of DUX4 protein that occurs in FSHD. We will ask if having both conditions (less Fat1 and more DUX4) leads to more severe symptoms than each one alone. Finally, we are also engineering mice that have genetic defects found in the FAT1 gene of FSHD-like patients and will ask if therapeutic correction of such mutations even after disease onset can lead to improving muscle performance.

▶ **NOVEL ROLE FOR REDUCED RNA QUALITY CONTROL IN FSHD PATHOGENESIS**

Principal Investigators: Sujatha Jagannathan, PhD; Robert Bradley, PhD; and Stephen Tapscott, MD PhD, Fred Hutchinson Cancer Research Center

July 1, 2014-June 30, 2016

Amount requested for project: $116,725 over two years (FSH Society Dotty Lynch Memorial Postdoctoral Fellowship Grant)

Does FSHD involve a failure of quality control?

By Sujatha Jagannathan, PhD

When healthy muscle cells grown in the laboratory are forced to make the FSHD-causing protein DUX4, they die catastrophically. Studying these dying cells can offer a glimpse into the molecular events set in motion by DUX4 that culminate in cell death.

To this end, we developed engineered muscle cells that express

. . . continued on page 16

ANNUAL RESEARCH REPORT

BASIC SCIENCE AWARDS

. . . from page 15

DUX4 synchronously upon addition of a small-molecule inducer. The reasons for developing this new system are twofold: When only one in 1,000 cells expresses DUX4 at any given time (as is the case with cells isolated from FSHD-affected individuals), any signal from the sick cell is drowned out by the noise from the healthy cells surrounding it. Even if we do isolate those cells that express DUX4, they still represent a heterogeneous mix of cells that each turn on DUX4 expression at different times, making the chronological ordering of the molecular events triggered by DUX4 difficult, if not impossible.

Our experimental system sidesteps the complex genetic mechanisms that cause DUX4 to be expressed in only a subset of the muscle cells in individuals with FSHD by placing DUX4 under the regulation of a defined system that can be turned on and off at will. This allows us to investigate molecular mechanisms that may be activated or deactivated as a result of DUX4 expression at a given point in time and how they relate to the events that happened prior to that time and those that follow.

Studies such as ours are particularly important in light of recent discoveries that suggest that expressing DUX4 at a single point in time still causes the cells to die later, even when they no longer express DUX4. Hence, defining the temporal sequence of cellular events triggered by DUX4 expression could be key to developing effective therapeutics for FSHD and is the overarching goal of my work.

One pathway that is particularly interesting to us is a quality control mechanism in the cell called nonsense-mediated RNA decay (NMD). NMD ensures that messenger RNAs (mRNAs) that form the template for cellular protein synthesis are free of errors. We recently discovered that DUX4 inactivates NMD by destroying one or more key proteins involved in this process without affecting their RNA levels (Feng et al., 2015, eLife).

This result was surprising to us on many levels. First, despite being a transcription factor whose function is to induce RNA synthesis (also called transcription), DUX4 could apparently affect protein level changes in the cell without changing the RNA level of the corresponding protein.

Second, if the defective RNAs, now stabilized because of the inability of DUX4-expressing cells to efficiently degrade them, are in fact translated, the cell could be flooded with defective and toxic protein products, explaining DUX4's cytotoxicity. However, given the complexity of the events that ensue upon DUX4 expression, it is imperative to place NMD inhibition in the context of the other events in the cell and ask what triggers it and how much of the toxic effect of DUX4 is contributed by NMD inhibition.

To answer these questions, we measured the RNA and protein composition of cells using high-throughput RNA sequencing and mass spectrometry at early and late time points following DUX4 expression until cell death (which takes about 16 hours in our system). We found extensive protein level alterations in DUX4-expressing cells that are not accompanied by a corresponding change in RNA level, indicating that DUX4 does indeed modulate gene expression at the post-transcriptional level. Moreover, preliminary evidence indicates that the defective RNAs that accumulate in DUX4-expressing cells due to NMD inhibition are, in fact, translated into potentially defective proteins.

We are currently working to confirm and extend these findings. We hope that by placing as many pieces of the puzzle that is DUX4-induced cell death in their right place, we can eventually find a way to intervene with the progression of DUX4-induced cell death and muscle loss.

From left to right, Suja Jagannathan, Lauren Snider, and Qing Feng are members of the Tapscott-Bradley lab who are involved in this project.

PHYSIOLOGICAL STUDIES OF MUSCLE WEAKNESS IN FSHD

Principal Investigators: Jun Udaka, MD PhD, and Charles Emerson, PhD, University of Massachusetts Medical School, Worcester

$212,060 for two years (FSH Society Helen Younger and David Younger Research Fellowship)

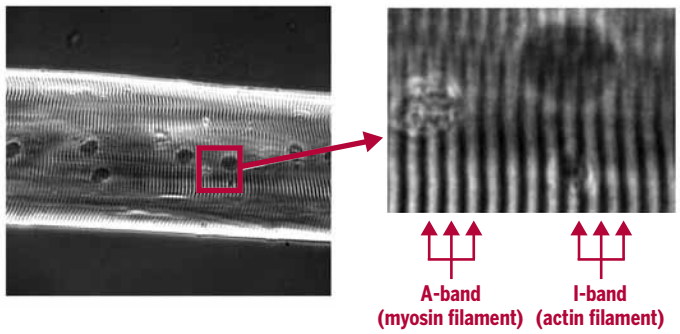
FSHD muscle fibers appear to be more sensitive to calcium signaling

By Jun Udaka, MD PhD

The pathophysiology of FSHD is poorly understood and understudied. To address this need, our studies are designed to identify physiological and biochemical differences between FSHD and healthy muscle to explain why specific muscles in FSHD patients are weak.

Special machines with highly sensitive mechanical sensors allow us to measure the contractile properties of single muscle fibers, which are the contractile cells in muscles. Studying single muscle fibers is very useful for a disease such as FSHD, in which specific muscles such as the bicep show profound weakness, whereas other muscles such as the deltoid appear to function normally.

Our preliminary findings reveal that muscle fibers from bicep muscles of FSHD patients on average have higher calcium



Skinned muscle fiber from a FSHD patient is examined for abnormalities. Light and dark colors are the result of differences in how light is refracted by fibers containing primarily actin versus myosin. The distance between dark and light bands is approximately 2.5 micrometers (millionths of a meter).

(Ca2+) sensitivity relative to fibers from control bicep muscles of unaffected subjects. This finding suggests that specific molecular components of the calcium regulatory contractile apparatus in fibers are not functioning properly.

Our next step is to identify the specific proteins in FSHD fibers that are responsible for this abnormal calcium regulation. To accomplish this goal, we are using mass spectrometry proteomics technologies, a powerful tool that enables us to identify and quantitatively compare all the proteins expressed in the same FSHD and control muscle fibers that we analyze in our single fiber assays physiologically.

Additionally, these proteomics technologies enable us to determine the phosphorylation status of contractile proteins, which has a key role in the regulation of calcium sensitivity.

We expect that our findings will enable us to develop therapeutics targeted to treat FSHD disease pathology and improve muscle function in FSHD patients.

▶ AUTOPHAGY DEFECTS IN FSHD

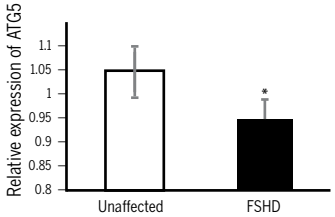
Principal Investigator: Sachchida Nand Pandey, PhD, Children's Research Institute, Washington, DC
$99,599 over two years

More than autophagy may be involved in FSHD

By Sachchida Nand Pandey, PhD

Autophagy is an important cellular process that keeps cells in homeostasis by cleaning the damaged or unwanted organelles and materials. Imbalanced autophagy activities in cells have been associated with many diseases.

In skeletal muscles, a basal level of autophagy activity is required to keep our muscles healthy. Excessive autophagy activities cause muscle wasting, whereas insufficient autophagy activities contribute to muscle diseases such as collagen VI myopathy.



Lower expression of autophagy protein 5 (ATG5) in FSHD myoblasts (n=4,*p,0.05)

Using protein assays to determine the amount of several proteins involved in autophagy activities, we discovered that these proteins expressed at different levels in FSHD myoblasts compared to control myoblasts, suggesting lower autophagy activities in FSHD. The evidence includes lower expression of proteins that are involved in forming autophagosomes, which are organelles performing the autophagy process.

We further explored the autophagy process using myoblasts from three additional pairs of patients with FSHD and their healthy siblings. The data validated our original finding of lower autophagosome formation. However, we observed variations in the number of proteins that were accumulated in the cells from different patients. Our findings suggest that other molecular mechanisms are contributing to the protein turnover in addition to the autophagy activities in FSHD myoblasts.

We are currently investigating the involvement of proteasomes and whether DUX4 is responsible for the lower autophagy activities.

▶ PROTEIN CHEMISTRY AND PROTEIN-PROTEIN INTERACTIONS OF DUX4

Principal Investigator: Jocelyn Eidahl, PhD, The Research Institute at Nationwide Children's Hospital, Columbus, Ohio
$70,000 over one year (FSH Society Marjorie Bronfman Postdoctoral Fellowship)

Identifying DUX4's partners in crime

By Jocelyn Eidahl, PhD

DUX4 is the candidate therapeutic target for treating muscle damage in people with FSHD. Our lab is dedicated to studying the DUX4 protein to uncover biochemical properties that, when inhibited, disrupt its activity in FSHD muscle. We believe DUX4 could be interacting with other proteins through one of these regions that then influences its ability to cause muscle damage. Our studies have identified protein candidates able to associate with the DUX4 protein. We have studies underway to determine if these interactions are essential for DUX4-associated damage.

Additionally, we have demonstrated that DUX4 is subject to chemical modifications that could be altering its activity in muscle. After proteins are synthesized, chemical modifications can occur that alter its location in cells, ability to bind other biological molecules/proteins, or even its stability.

Our proposed research plan is to focus on how and why these modifications occur. Ultimately, if we determine DUX4 is working with additional proteins or is subject to a modification that affects DUX4 protein activity, we can then begin to develop therapies to prevent these events and muscle damage in FSHD patients.

We are hopeful that our research will uncover important details about the role of DUX4 in muscle damage and help aid in developing treatments for FSHD.

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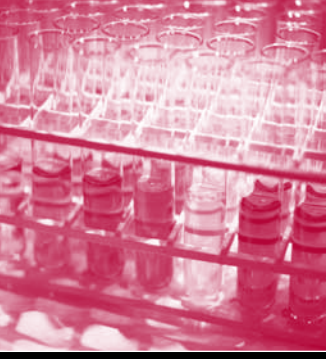


ANNUAL RESEARCH REPORT

CLINICAL TRIAL READINESS

Critical steps in the path to treatment

by **JUNE KINOSHITA and DANIEL PAUL PEREZ**

In addition to funding early-stage drug discovery research, the FSH Society invests in "clinical trial readiness" projects to develop and validate biomarkers and clinical trial outcome measures. We also keep up a steady drumbeat urging patients and unaffected family members to join the FSH Society so that they can be notified of important clinical studies and drug trials that need volunteers.

Such projects may not seem as "glamorous" as drug discovery, but they are absolutely critical. These tools and resources are the standards by which drug developers will decide whether FSHD is "trial ready." The more effort we put into tools that reduce the risk of running a clinical trial, the more willing biotechnology and pharmaceutical companies will be to invest in developing treatments.

▶ EVALUATION OF AN FSHD-SPECIFIC PATIENT-REPORTED OUTCOME MEASURE AND A DISEASE-SPECIFIC FUNCTIONAL RATING SCALE

Principal Investigator: Jeffrey Statland, MD, University of Rochester, New York

$55,597 over two years; $43,666 year one, $11,931 year two (FSH Society Marc and Helen Younger Research Fellowship)

New tools for measuring clinical outcomes

By Jeffrey Statland, MD

Our research group specializes in designing tools to conduct high-quality FSHD clinical trials. The aim of this proposal is to test the reliability, relationship to FSHD severity, and responsiveness to change of three new FSHD outcomes: 1) a disease-specific patient-reported health inventory (FSHDHI); 2) a disease-specific functional rating scale (FSHDFO); and 3) a new technique for measuring changes in muscle structure, electrical impedance myography (EIM).

The FSHDHI was developed from large-scale survey input from 328 FSHD patients including 48,000 direct patient responses. Individual questions for the patient-reported questionnaire were screened and selected based on their reported high prevalence and importance to people with FSHD.

The FSHDFO, on the other hand, took each of these high-impact areas and combined existing standardized measures of motor function into a comprehensive FSHD-specific battery of tests.

EIM uses a low-intensity electrical current to obtain information about underlying muscle structure. Initial analysis suggests a relationship between measurements made using EIM and FSHD disease severity.

Our study is currently completing recruitment, and we expect to have all of our follow-up visits completed by September 2016. The seed grant from the FSH Society enabled us to obtain money from the NIH to complete the development of the FSHDHI and to collect the necessary pilot data to submit an NIH grant to validate EIM at multiple sites across the U.S. At the end of our studies, we hope to have three new disease-relevant outcome measures for future FSHD clinical trials.

Electrical impedance myography. A portable device (Skulpt Inc., Boston, Mass.) with a simple, handheld wand is used to measure impedance over selected muscles.

▶ DEVELOPMENT OF A NOVEL CHIP-BASED DIAGNOSTIC ASSAY FOR FSHD

Principal Investigators: Kyoko Yokomori, DVM PhD, University of California, Irvine, and Shohei Koide, PhD, The University of Chicago, Illinois

$40,000 for one year

A novel diagnostic assay based on epigenetics

By Kyoko Yokomori, DVM PhD

Our laboratory focuses on the epigenetics of FSHD. Genetic information encoded in the form of DNA wraps around "histone" proteins to form "chromatin" fibers in the cell nucleus. Histones, as well as DNA, are subject to specific chemical changes (so-called "epigenetic modifications") that determine how genetic information is expressed from DNA. With generous support from the FSH Society, we previously demonstrated that FSHD is an "epigenetic abnormality" disorder characterized by loss of a normal histone modification (histone H3 lysine 9 tri-methylation [H3K9me3]) at D4Z4 repeat regions.

As summarized in the figure below, we recently also found that 1) the loss of H3K9me3 at D4Z4 results in the loss of SMCHD1 binding (mutations in the SMCHD1 gene are linked to FSHD2 and severe cases of FSHD1) and increased DUX4 expression; and 2) although there are D4Z4-like repeats on many other chromosomes, they do not encode functional DUX4 protein, and H3K9me3 found in those repeats remains unchanged in FSHD. These findings highlight the special role for the D4Z4 chromatin and the DUX4 gene on chromosome 4q in FSHD.

With further support from the FSH Society and the generous donation of blood samples from FSHD patients and families, efforts are ongoing to test the possibility that peripheral blood mononucleocytes (PBMCs) can be used to monitor the specific decrease of H3K9me3 as a non-invasive diagnostic method.

Further characterizing the cause and effect of epigenetic changes in FSHD, and possibly reversing these changes, would be the next step toward our goal to develop potential therapeutic strategies.

▶ FSHD CLINICAL TRIALS NETWORK WORKSHOP
Principal Investigator: Rabi Tawil, MD, University of Rochester Medical Center, New York
May 2015; $25,000

Workshop reviews progress and remaining challenges

By June Kinoshita

Thirty-six participants from seven countries representing academic centers, funding and regulatory agencies, and pharma and advocacy groups met May 29-30, 2015, at the University of Rochester for a workshop on clinical trial preparedness in facioscapulohumeral muscular dystrophy (FSHD). The potential for targeted clinical trials in the near future has heightened the interest of researchers and pharma in FSHD trial readiness.

The workshop has now been published: Clinical trial preparedness in facioscapulohumeral muscular dystrophy: Clinical, tissue, and imaging outcome measures. 29–30 May 2015, Rochester, New York. Rabi Tawil, George W. Padberg, Dennis W. Shaw, Silvère M. van der Maarel, Stephen J. Tapscott, The FSHD Workshop Participants. *Neuromuscul Disord.* 2015 Nov 9. pii: S0960-8966(15)30028-6. doi: 10.1016/j.nmd.2015.10.005.

See our Spring/Summer 2015 issue for a more detailed report.

▶ MICRODIALYSIS FOR THE STUDY OF INFLAMMATORY FEATURES IN FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY
Principal Investigator: Giorgio Tasca, MD, Institute of Neurology, Catholic University School of Medicine, Rome, Italy
$70,000 over one year

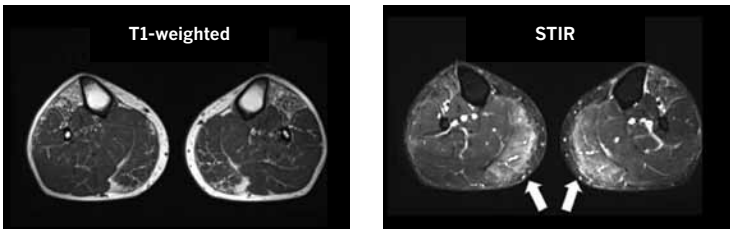
Probing muscles for inflammatory biomarkers

By Giorgio Tasca, MD

Our project is in the framework of a research area of our group that aims at understanding the inflammatory mechanisms in this disease.

This study started one year ago as the development of a new method to monitor the muscle microenvironment by using minimally invasive, fine needles embedded in FSHD-affected muscles of patients. The needles enable us to draw fluid samples over several days, which we are analyzing in the hopes of discovering potential new biomarkers of disease.

So far, the procedure has been performed in most of the patients and controls, and only a few individuals still need to be recruited to reach the goal of the expected number of subjects. The procedure has been safe and very well tolerated, and no adverse events have been reported. A preliminary analysis gave us encouraging results about the feasibility of this protocol.



Muscle magnetic resonance images of the calves in one FSHD patient. On the left (T1-weighted sequences), the white color corresponds to areas of fatty degeneration of the muscles. Vice versa, white areas on the corresponding right image (STIR sequences), marked by arrows, represent areas of active disease that can be identified by MR imaging before fatty degeneration takes place. Our microdialysis procedure targets these latter muscles, with the objective to understand the early stages of tissue damage.

We believe that an accurate characterization of the role of inflammation and of tissue alterations in early stages of disease at the single-muscle level will be able to provide useful insights to further clarify FSHD pathophysiology and bring us closer to the development of targeted treatments.

The next steps for us will be to complete the recruitment of this study and to analyze the full results. We are confident we will reach these objectives in the next few months. Future perspectives will describe the application of other techniques and protocols of analysis to the interstitial fluids obtained during this study.

▶ DEVELOPMENT OF A NEW METHYLATION ASSAY FOR FSHD DIAGNOSIS
Principal Investigator: Giancarlo Deidda, PhD, Institute of Cell Biology and Neurobiology, Rome, Italy
$56,000 for 18 months

A new method to diagnose and study FSHD

By Giancarlo Deidda, PhD

This disease is linked to an epigenetic modification at the chromosome 4q subtelomere caused by the contraction of the D4Z4 macrosatellite array in FSHD1, or by functional impairment of SMCHD1 in FSHD2. Both genetic defects lead to D4Z4 DNA hypomethylation associated with the inappropriate expression in skeletal muscle of the DUX4 transcription factor. It has been shown that the expression of DUX4 in FSHD also requires the presence of a polymorphic polyadenylation signal (PAS) distal to the last D4Z4 unit (4qA).

We analyzed the methylation levels of the region immediately distal to the D4Z4 array critical for FSHD development and set up

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ANNUAL RESEARCH REPORT

TOWARD TREATMENT DISCOVERY

Tools and techniques for silencing DUX4

by JUNE KINOSHITA and DANIEL PAUL PEREZ

The FSH Society is supporting research projects that employ various strategies to block expression of the DUX4 gene, which is a leading candidate for the cause of FSHD. In addition, the Society is interested in supporting research to develop new experimental models—cell and tissue cultures and animals—needed to better understand the disease process, screen drugs, and test how well the strategies work.

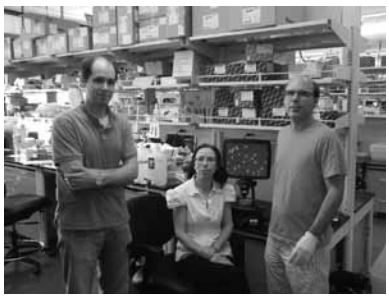
EXPLOITING GENOME EDITING TECHNOLOGY TO MODIFY AND REGULATE THE FSHD DISEASE LOCUS

Principal Investigator: Michael Kyba, PhD, Lillehei Heart Institute, University of Minnesota, Minneapolis

From 2015; $125,000 over one year

Targeting the 4qA allele so that DUX4 can't be expressed

By Michael Kyba, PhD



From left to right, Erik Toso, Lynn Hartweck, PhD, and Michael Kyba, PhD

FSHD is a genetic disease, which means it is caused by an alteration in the DNA sequence of an affected individual. Experimental approaches currently in design to treat the disease involve trying to reverse or ameliorate the effects of this mutation on the regulation of a gene at the FSHD locus named DUX4, or on blocking the activity of the DUX4 protein.

Although such approaches are feasible and very worth pursuing, it is also intriguing to consider the possibility of altering the genome itself to convert the DNA sequence that encodes susceptibility to FSHD into one that encodes normal muscle function.

About 30 years ago, the first experiments were undertaken in which targeted changes to the genome of mammalian cells were introduced. These involved directing changes in the genome by inserting DNA corresponding to the new desired sequence. However, these methods were extremely inefficient, succeeding in only one cell out of several million.

In the last decade, methods of making this process more efficient have been developed. These new methods result from the discovery that breaking the DNA double helix at a specific sequence dramatically increased the rate at which a directed change could be made to that sequence. As the cell tries to repair the break, if it is provided with a template sequence that includes a modification, it will often incorporate that modification into the repair, and hence the sequence of the genome at that site will be changed.

Although the knowledge that DNA breaks enable targeted sequence changes was encouraging, making DNA breaks occur where and when you wanted them was out of reach. Until very recently, that is.

In the past few years, methods of designing proteins that bind to specific DNA sequences have been perfected. These DNA-binding proteins can be made to bring in a nuclease, a protein that can break the DNA and thus enable template-directed DNA sequence changes. This research project aims to use this new technology to alter the DNA sequence in cells bearing FSHD mutations.

Unlike many other genetic diseases, FSHD is not caused by small, so-called "point mutations" that change a single letter of the DNA code. Rather, FSHD is caused by the deletion of hundreds of thousands of nucleotides, or letters of the DNA code. Therefore, it is not straightforward to reverse the mutation.

However, in addition to the large deletion, FSHD requires that the deletion be in the context of a specific surrounding sequence. This surrounding sequence comes in two flavors: permissive and protective. All FSHD-affected individuals carry the deletion within the permissive sequence. Rather than reversing the large deletion, our approach is directed toward converting the permissive sequence to a protective sequence.

In the first year of this research project, we developed tools that allow targeting of a nuclease to the permissive surrounding sequence. We tested these tools and determined that they actually result in DNA breaks at this sequence and do, in fact, enable the desired template-directed changes. We continue to work to characterize cell lines in which the permissive 4qA allele has been altered.

INVESTIGATING EFFECTS OF PARP1 INHIBITORS IN DUX4 EXPRESSION

Principal Investigator: Yi-Wen Chen, DVM PhD, George Washington University and Children's National Medical Center, Washington, DC

$89,267 over two years

Investigating PARP1 as a potential therapeutic target for FSHD

By Yi-Wen Chen, DVM PhD

Expression levels of genes are regulated by a group of proteins called transcription regulators. Each gene is regulated by many transcription regulators via different molecular mechanisms. While we know that aberrant expression of double homeobox protein 4 (DUX4) causes FSHD, it is not clear how the expression of DUX4 is controlled by these transcription regulators in our cells.

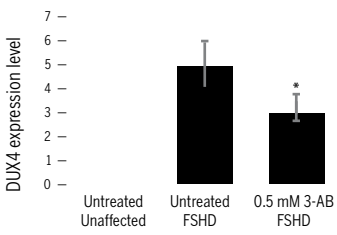
Understanding how DUX4 expression is regulated and identifying specific regulatory proteins that control DUX4 expression will help us develop therapeutics to suppress the pathogenic DUX4 expression in patients' cells.

Yi-Wen Chen, DVM PhD

Our proposed studies aim at studying a protein called poly (ADP-ribose) polymerase 1 (PARP1) and its role in regulating DUX4 expression. In addition, we explored the possibility of suppressing DUX4 expression in patients' muscle progenitor cells (myoblasts) using inhibitors of PARP1.

Our data showed that PARP1 inhibitors suppressed expression of DUX4 in cultured FSHD myoblasts. In addition, this effect may involve an enzyme that regulates DNA methylation in the genomic region where DUX4 is located.

We are currently testing the PARP1 inhibitors in a mouse model that expresses DUX4. The findings will help us determine whether PARP1 inhibitors can suppress DUX4 in vivo and should be further investigated as a potential treatment for FSHD.



DUX4 expression is reduced in FSHD myoblast cells treated with a PARP1 inhibitor (3-AB).

▶ BET PROTEINS AS THERAPEUTIC TARGETS IN FSHD

Principal Investigator: Francis M. Sverdrup, PhD, Center for World Health & Medicine, Saint Louis University, Missouri

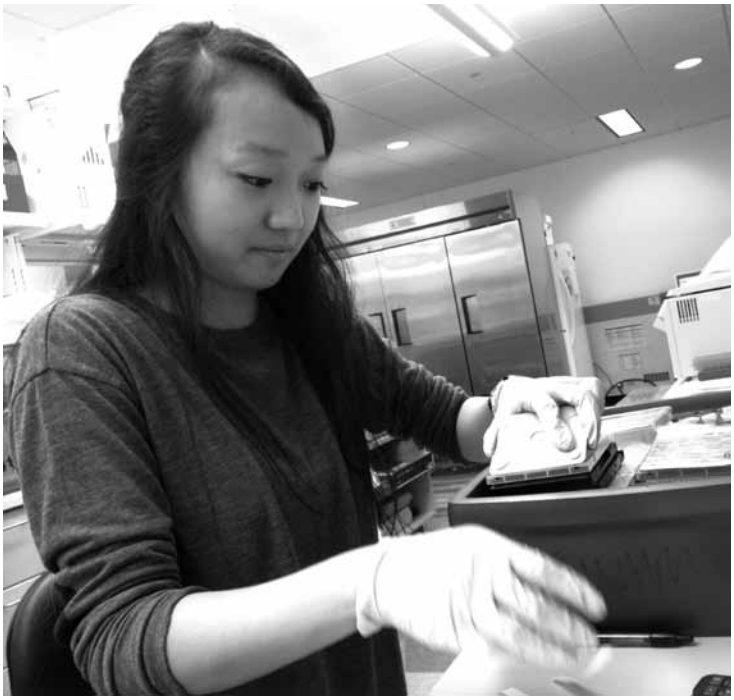
August 1, 2014-July 31, 2015; $51,425 for one year (FSH Society William Michael Postdoctoral Fellowship Grant)

Placing a BET on shutting down DUX4

By Francis Sverdrup, PhD

Our center, staffed by members with broad experience in the pharmaceutical industry, is focused on drug discovery for rare and orphan diseases. We are intensely interested in translating the basic discoveries about FSHD disease mechanisms into potential new therapies.

We have identified a class of drug-like molecules termed BET bromodomain inhibitors that turn off the toxic DUX4 gene that is the hallmark of FSHD. Through funding provided by the FSH Society, we have identified the specific target of these drugs, the BET protein BRD4, which plays a major role in turning on DUX4. These data provide new insights into how DUX4 is turned on and point to ways in which we can design better drugs for turning off DUX4.



Shannon Tai, undergraduate student, at work in the Sverdrup lab

We are very excited to take the next step to treat mice containing human FSHD muscle cells with BET-inhibiting drugs to determine if we can turn off DUX4 within animal muscle tissue. These are critical activities that will get us closer to testing BET inhibitors in human clinical trials.

▶ GENE SURGERY USING TALEN TECHNOLOGY: A THERAPY FOR FSHD

Principal Investigator: Julie Dumonceaux, PhD, Institut de Myologie, University of Paris, U974-Inserm, France

$117,500 over one year

Gene surgery to disable DUX4 expression

By Julie Dumonceaux, PhD

Unlike classical genetic diseases in which the expression of a gene is lost due to a mutation (as in the vast majority of other neuromuscular disorders), FSHD seems to result from increased

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For a Good Time, Call Sacramento

Plans to meet quarterly

by WILLIAM LEWIS III, MD
Davis, California

A new support group met for the first time in Sacramento, California, on August 19 at a centrally located restaurant. We had 10 attendees from the larger Sacramento area. About half the attendees were affected by FSHD, and the other half were family members. Ages ranged from the 20s to retired.

The group was really positive and fun. We introduced ourselves and spoke of when we were diagnosed, affected and unaffected family members, and how we were all still being very active socially and professionally. One member thought the group might be more of a grief counseling group but was thrilled to find that we were quite jocular. (Thanks, Tim and Dave! Keep up the good work.)

I suggested that we form a band, as many members were/are musicians. I thought harmonica might be good! (Y'all should get the joke.)

The group suggested that we begin as a social group and throw in FSHD information as part of the agenda. The University of California Davis Medical Center is in our area and has an active muscular dystrophy clinic. We will ask a member of the UCD Physical Medicine and Rehabilitation Department to attend the next meeting, as there were many questions about assistance/mobility devices, insurance coverage, tax write-offs, etc.

Karen Dunkerly, who suggested the formation of the group, was "volunteered" to be the organizer for the next meeting. We decided that a quarterly meeting would be good and met again in early November. We are sure the group will grow as word gets out, so anyone interested should contact the FSH Society to be added to our roster. FSHWatch

Editor's note: The author is a member of the Board of Directors and Scientific Advisory Board of the FSH Society.

FSH Society Ambassador Is Ms. Wheelchair USA

SKYLAR CONOVER'S INSPIRING STORY WINS HER THE CROWN

Our very own FSH Society Ambassador Skylar Conover, from Allen, Texas, was crowned Ms. Wheelchair USA on July 18 at the national pageant in Cuyahoga Falls, Ohio. Linda Laurello-Bambarger, a member of our Board of Directors, was there to cheer her on and receive a $5,000 donation to the FSH Society from Munzee, one of Skylar's sponsors. Congratulations, Skylar!! You are an inspiring young woman and a great advocate for the FSHD and disabled communities.

Skylar Conover (center) is Ms. Wheelchair USA.

AN INTREPID SCOOTER RIDE RAISES AWARENESS AND FUNDS

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I should be able to travel distances of 35 miles or so each day.

This got me to thinking, and I eventually decided I would raise awareness of FSHD by traveling from New York City to the West Coast on my scooter. Furthermore, Gracie would come with me. We would raise donations online, primarily by establishing a presence on social media.

Up until that time, I didn't even have a Facebook account. Nevertheless, I began to announce to my friends and on my new Facebook account my intention to do a coast-to-coast fundraiser, in my mind entering into a social contract that would commit me to following through.

As my April departure date approached, I became more concerned about the logistics of such a long trip and had concerns about the potential to raise funds. As a result, I decided I would scale down and do a smaller event on this first occasion. This would be a trip from New York City to Washington, DC.

In preparation, we scheduled a test run for early June. With the help of Rob Dye, my longtime good friend from Austin, Texas, we completed a five-day trip from Central Park in New York City to the Liberty Bell in Philadelphia. I used Google Maps selected for bicycles to plot the route. Rob drove the van, shot video, cycled at times, and traveled with Gracie in the van when she wasn't running with me.

The whole trip went just as planned. Gracie ran with me for 8 to 10 miles per day, and we rolled into Philly on the afternoon of the fifth day. This trip provided some important insights and reassured me that I could do repeated days of long scooter travel without becoming too exhausted to continue—something I wanted to be certain of before asking for donations or other financial support.

Rob offered to drive again for the New York City-to-DC trip and suggested starting over the Labor Day weekend so he could add the Monday holiday to his vacation days. He arrived in New York the Friday before Labor Day, and we spent Saturday going over logistics and making final preparations.

On a gorgeous Sunday morning, we loaded the scooters and Gracie in the van and drove from my home in Yonkers, NY, to Columbus Circle in Manhattan. After chatting for an hour with a small group of friends and supporters, we set off through Central Park, accompanied by my friend Ken Jones on bicycle.

On leaving the park, we all headed west to Riverside Drive and continued north toward the George Washington Bridge, stopping along the way near Columbia Medical School for lunch at a falafel truck. Ken, Gracie, and I continued over the GWB to Fort Lee, where we met Rob and the van. After this initial 11-mile stretch, I left Gracie and the others and continued on my own through north Jersey, reaching Newark about 6:30 that evening.

Along our travels we looked for opportunities to engage with people to tell them about FSHD and our fundraiser. Gracie was helpful in this regard, and I used any occasion when someone said, "Oh, what a beautiful dog you have there!" to thank them and then ask, "Can I tell you what we're up to?" This often led to a conversation and allowed me to give out our business card with FSHD information and the links to our Facebook page.

In terms of reach, this was not really an effective way to introduce FSHD to a wider audience. For that we needed either to go viral on Facebook or get some additional media coverage.

We reached Philadelphia on Thursday in the pouring rain. It was sunny again on Friday, which was scheduled as a non-travel day. While going down Market Street we came across the FOX 29 offices and decided to pitch our story. I called the number provided at the front desk and, after summarizing our story, was told there would be an editorial meeting in 30 minutes and that I would hear back shortly if they wanted to cover the story.

While enjoying a delicious Philly cheesesteak at Sonny's and getting some valuable social-media insights from a Florida couple we had just met, we received a call from FOX. They wanted to send a team to cover our story. We greeted reporter JoAnn Pileggi and photographer Martin Reiman in front of Sonny's, and for the next couple of hours they talked with us and took video of Gracie and me traveling along the streets of downtown Philly. The interview aired that evening on the 6 o'clock news, and the next day several drivers honked and even stopped to give me a donation, saying they recognized us from the news.

We decided to use the same direct approach with the news media in Baltimore. While traveling along U.S. Route 40 from Aberdeen, Rob made calls and contacted reporters for the Baltimore media via Twitter. This resulted in WMAR, the ABC affiliate in Baltimore, sending a photographer to do an interview along the highway, which appeared on the news that night.

Meanwhile, as we later learned, JoAnn Pileggi was contacting her colleagues in our nation's capital to tell them about our trip. That afternoon we received a call from FOX 5 in Washington inviting us to a studio interview on their Friday morning program.

To be ready for a Friday morning interview, we abandoned our scheduled rest day in Baltimore and continued on. We arrived in Washington on Thursday afternoon, touching the base of the Washington Monument at the 300-mile mark.

That evening, Rob and I had a long discussion about how to approach the interview, trying to decide what points I should try to make if given the opportunity. We decided that FSHD awareness would be well served if I could convey three things: 1) MD and MS are different diseases, MD a disease affecting skeletal muscle, and MS a disease of the central nervous system; 2) MD is not a single disease, but a category that encompasses nine distinct diseases affecting muscle; and 3) symptoms of FSHD may appear initially in the face, scapulae, and humerus muscles, but the disease progresses to affect all skeletal muscle and results in profound weakness.

As it turned out, the flow of the interview was entirely out of my hands, and there was no opportunity to mention these specific items. Nevertheless, our gracious interviewer, Maureen Umeh, devoted nearly five minutes to our discussion about FSHD and how it affects individuals, as well as preparation for Gracie's participation in the fundraising trip.

Doug & Gracie NYC to DC raised over $19,000 for the FSH Society and exposed television viewers in three major media markets to FSHD muscular dystrophy.

Logistically, everything went as planned, with no mechanical issues, no weather-related delays, and no exhaustion. Gracie took it all in stride and had a wonderful time.

Rob, Gracie, and I drove back to New York with a satisfying sense of accomplishment, thinking about how to apply the lessons from this adventure to something on a larger scale next year. FSHWatch

A Teen Inspires Others

4H auction raises funds for the FSH Society

by MARLA FARBACHER
West Jefferson, Ohio

My son Ben is 17 years old and entering his senior year of high school. He attends West Jefferson High School and is enrolled in the firefighting program at Tolles Career and Technical Center. After high school, he intends to attend community college so he can get his paramedic certification. He then plans get his bachelor's degree in nursing.

Ben was first told of his suspected diagnosis of FSHD in May of this year. It was confirmed by a DNA test in June. Ben and his younger brother Thomas participate in 4H here in Madison County. This year, Ben raised a hog and a goat. His brother also raised a hog. At the fair, the animals are pre-sold at the market price. That money then goes to the kids who raised them.

On the last day of the fair, there is an auction for the animals. The people who bid on the animals don't actually acquire them; the bidders are area business and community members who are supporting the kids and the 4H programs. That money also goes to the kids. It is customary for the kids to donate a portion of their total proceeds to a charity. Kids typically donate 5 to 25 percent to various causes.

This year, Ben chose to donate 100 percent of the proceeds of both of his animals to the FSH Society. His brother donated 50 percent. The kids each stand up during the auction, and their name, their 4H group, their animal, and their charity are announced. When Ben's charity and percentage were announced, it was briefly mentioned that this was due to his recent diagnosis.

After the fair, two teenagers, Dylan Wildman and Avery Haley, approached us to donate money in honor of Ben. Several other kids followed suit and donated a percentage to the FSH Society. To date, they have raised about $2,500.

While Ben cannot lift weights anymore, he is still planning to play football this fall. We will be on the sidelines, trying not to cry. Ben's attitude about his FSHD is that he is optimistic that there will be a cure soon. He wants to do what he can to help make sure this happens. FSHWatch

Ben and Thomas Farbacher are all smiles over the success of their 4H auction.

Product Review: BBraver Handrims

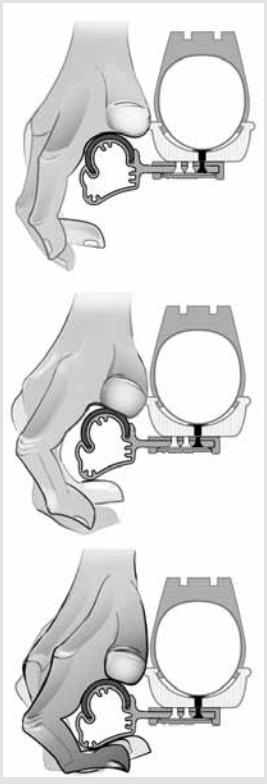
DESIGNED FOR BETTER GRIP AND COMFORT

A friend of mine, a former surfer and snowboard manufacturer, broke his back in a ski accident. His experience using a wheelchair made him think there must be better ways to design wheelchair handrims, as they are the interface between the body and chair.

Thus, the BBraver handrim was born. The idea is to improve grip and comfort. The top is covered with a grippy material, and the underside where you put your fingers is better shaped for your hand.

About a year ago, I got my hands on a pair of BBraver handrims. I felt about 30 percent stronger, with increased torque and overall better maneuverability. They dramatically changed my rolling life for the better.

For those of us who have less upper body strength, the difference is massive. My old steel handrims sucked the juice out of my arms too quickly. I can now go places I previously could not. A bonus is also the look and feel of the rims: amazing finish, different colors, and not so cold to the touch.



Until the end of 2015, BBraver is offering a 25 percent discount to those of us with FSHD. The handrims can be ordered online and delivered anywhere in the world. They currently fit Spinergy wheelchair wheels, the most common active wheelchair wheels in the world. One can also order complete wheel-handrim combos.

Shop and information: *https://www.bbraver.com/*. If you get some, let me know what you think. You can write to me at *calle@methodmedia.net*.

–Calle Eriksen, Stockholm, Sweden

WHAT FSHD HAS GIVEN ME

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hobbies you can find.

I threw myself into art and writing, and found that I have somewhat of a talent for both that I am working on further developing. Negative emotions are hurtful, but you can put them into words that others may relate to, let them flow through a paintbrush, or sing them for a loved one.

There is still a beautiful life that you can fit into just as easily as anyone else, and you are no lower than anyone else just because maybe you need help reaching for that cup on the top shelf.

You have a unique perspective as a person with muscular dystrophy. You may possess a greater appreciation of the simpler things in life, or be less judgmental as you understand that all people have their own struggles in life, and that just because you can't always see or understand them does not mean they do not exist.

You may be more compassionate due to the fact that compassion toward yourself is greatly appreciated, so that when people ask for help, it might mean the world to them just as my friends piggy-backing me up hills without annoyance or frustration means the world to me.

You may develop better coping skills from having to deal with so much yourself on a daily basis.

I struggled many years with worry about what I later discovered were rather silly things. People who truly love you do want to help you, even if they don't always know the right way, the right things to say or do. While I was generally embarrassed and felt sometimes annoying, I've been told many times things like, "It's not even a big deal. It's cute anyway! I'd give you piggy-back rides regardless if you wanted."

It takes courage to be open. Walking in public places might get you many stares or whispers. I've heard countless mentions of how thin I am, or how my gait is slightly off. While it is sometimes hurtful, I've learned to either address the situation by using it as an opportunity to politely educate someone, or simply ignore it. What others say of you says more about them than it does about you.

Some people simply haven't heard of muscular dystrophy. It doesn't necessarily mean they are uncaring or cruel. A girl I once sat by in a class of mine used to tell me nearly every day that I should eat more because I looked sickly. For several weeks I either laughed it off or mumbled back things like, "Yeah, maybe."

After a while, I finally mustered the courage to tell her that I was only thin because of my condition, and I actually ate more than a man going through college. Not only did she feel extremely guilty (which wasn't my goal), but she also learned something new and started helping me gather my things after class, offering to carry my books if I needed.

Smile the best way you can

Never take situations like this personally; you are beautiful no matter your capabilities or your appearance. Living with any disease is hard. Muscular dystrophy has posed many obstacles for me, brought many tears, and made me question things I probably normally wouldn't have.

I am growing a greater appreciation for muscular dystrophy every day, however odd that may sound. It has taught me compassion, forgiveness, humility, courage, and appreciation. Life does not often go as planned, and we must learn to accept that and use it to our advantage.

So while people telling me to smile bigger has always bugged me due to the fact that I've lost some muscles in my cheeks, I urge you to smile in the best way you can.

It is okay to hurt, to cry, to feel sad and lazy some days. It will rain some days. Just remember the good weather, and know that it is coming. Don't be afraid to let others help you, and don't be afraid to offer your help to others.

I wish you much peace, plenty of love, and safety in your journey. FSHWatch

Reprinted with permission from *Muscular Dystrophy: A Concise Guide,* Springer 2015.

ANNUAL RESEARCH REPORT: CLINICAL TRIAL READINESS

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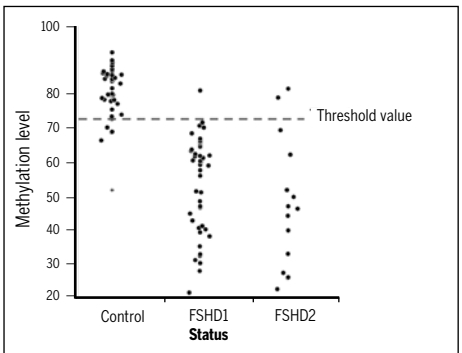
a methylation assay restricted to 4qA alleles that contain a PAS sequence, avoiding the interference of non-pathogenic arrays. We identified a small DNA region that is significantly different among FSHD1, FSHD2, and control subjects, resulting in the identification of affected individuals currently with a sensitivity of 95 percent, supporting the potential usefulness of this assay for FSHD diagnosis. Moreover, we are currently evaluating the relationship between this assay and disease severity, adding further information to the molecular diagnosis of FSHD.



Methylation values distributions at the PAS region in controls, FSHD1 and FSHD2 subjects. There is a minimal overlap of FSHD and control in the close proximity of threshold value.

We believe that this analysis may allow the establishment of a rapid and sensitive tool for FSHD diagnosis and improve the comprehension of molecular mechanisms of the disease. FSHWatch

WHEN MUSCULAR DYSTROPHY IS PERSONAL—AND GLOBAL

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had a discussion with a physiotherapist who taught him what he could do on his own at home.

Before coming to Boston, Chege said, he was not aware that any research on FSHD was being done in Africa; in fact, research is currently underway in South Africa.

But Chege would like to return to the U.S. in 2016 to attend the next conference on FSHD, only next time, he hopes to bring his sons along as well. FSHWatch

Reprinted with permission from WBUR. Source link: *http://commonhealth.wbur.org/tag/muscular-dystrophy*

Editor's note: Chris Chege contributed a story to *FSH Watch* in Spring 2014.

ANNUAL RESEARCH REPORT: TOWARD TREATMENT DISCOVERY

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A researcher in the Dumonceaux lab takes aim at DUX4.

expression of a gene called DUX4. Because of this, FSHD could be targeted by therapeutic strategies to diminish DUX4 expression.

For many years, the scientific community has been developing molecular tools to reduce gene expression. Several of these technologies are now coming of age, being capable of complete excision of a targeted gene, and so opening new opportunities in the search for therapies.

These tools are customizable molecular DNA scissors that enable the genome to be engineered by precise manipulation of the DNA in the nucleus of any cell. Basically, with these molecular scissors, genomic DNA can be cut and selected portions of DNA can be replaced or removed to safely alter one gene without damaging others. In collaboration with the Concordet lab (Paris, France), the Dumonceaux lab has developed such scissors targeting essential regions of DUX4.

The funding allocated by the FSH Society has enabled the recruitment of a postdoctoral researcher dedicated to this research, without whom the project could not be completed. Initial results obtained through experiments on cells isolated from FSHD patients are very promising, underscoring the incredible potential of this technology. We now need to confirm these results in further experiments. FSHWatch

ANNUAL RESEARCH REPORT: BASIC SCIENCE AWARDS

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▶ **DYNAMIC MAPPING OF PERTURBED SIGNALING UNDERLYING FSHD**
Principal Investigator: Peter S. Zammit, PhD, King's College London, United Kingdom
$137,798 over one year to 18 months

Probing how FSHD muscle gets damaged and repaired

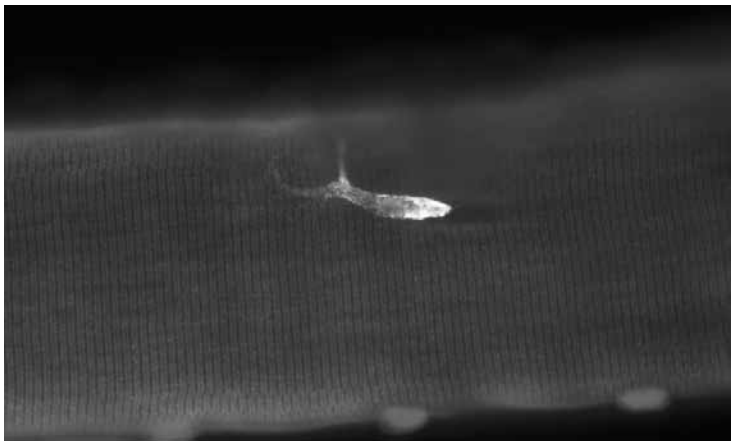
By Peter S. Zammit, PhD

Cells have carefully coordinated gene expression and signaling pathways that control all aspects of their function. Our lab combines experimental biology with sophisticated mathematical tools to investigate how muscle stem cells maintain and repair skeletal muscle.

With FSH Society support, we recently published a map of the signaling interactions within FSHD muscle by analyzing publicly available data on global changes in gene expression from FSHD patient muscle samples[1].

The overall aim is to discover signaling pathways that may be targeted by therapeutics to improve innate muscle repair in FSHD. We have identified several such targets and have been testing clinically approved drugs on one promising candidate, with encouraging preliminary results in improving muscle fiber formation from FSHD cells in culture.

Funding from the FSH Society also allows us to more deeply and accurately probe the process and control of muscle repair in FSHD, using patient-derived cells. We have filmed these FSHD muscle cells as they align and fuse to form multinucleated muscle fibers by using image analysis software that we developed. This reveals that the process is less effective than in healthy muscle cells,



A muscle stem cell in its niche on a striated skeletal muscle fiber

resulting in atypical muscle fibers, and has pinpointed critical points at which FSHD muscle repair deviates.

We have collected the RNA of muscle cells at these time points to map the underlying signaling to identify reasons for these perturbations. We are currently using state-of-the-art technology to measure changes in global gene expression, which will be analyzed by our new bespoke software. This will highlight potential new FSHD therapeutic targets, which will be investigated for their ability to improve natural muscle repair in FSHD. FSHWatch

Reference

[1] Banerji et al. (2015). ß-catenin is central to DUX4-driven network rewiring in facioscapulohumeral muscular dystrophy. J. R. Soc. Interface 12 (102). 20140797.

WHOLE-BODY MRI YIELDS NEW INSIGHTS

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muscle involvement can vary greatly among individuals. The KKI study demonstrated that WBMRI can detect muscle involvement in diverse parts of the body before loss of strength is discernible on physical examination.

MRI studies show that individual muscles in a single person can progress rapidly while the other muscles are spared. This may help to explain why, in many individuals with FSHD, we observe a slow progression of weakness punctuated by a much more rapid loss of strength at some point in their lives.

Early on, when a single muscle is affected, the patient may not experience a loss of strength because surrounding healthy muscles can compensate for the loss. But as these surrounding muscles are affected, they become less able to compensate, and we observe a gradual loss of strength. At some point, when a critical remaining muscle succumbs, we observe a more dramatic loss of strength.

The KKI study used "T1-weighted" imaging to identify the degree of muscle replacement by fat. In addition, using a technique called STIR (short T1 inversion recovery), the investigators could use MRI to detect muscles with edema (fluid infiltration), which they think represents an active inflammatory phase that precedes the replacement of muscle by fat.

Thirteen individuals (eight men, five women) were enrolled in the study. They ranged in age from 20 to 72, with a mean age of 48 years. All of these volunteers completed the study in its entirety, and no complications were reported. For each subject, from 92 to 118 muscles were visualized and given scores for fat replacement and edema-like abnormalities.

These volunteers varied considerably in their disease severity. The percentage of muscles that were affected in individual subjects ranged from 3 percent to 75 percent. The most frequently and severely involved muscle overall was the semimembranosus (one of the hamstring muscles in the back of the thigh). Muscles of the trunk (including the paraspinal muscles and muscles of the abdominal wall) were also among the muscles involved most frequently.

Conversely, several muscles were frequently spared in the study population. In all 13 volunteers, the following muscles were unaffected: the iliacus, obturator externus, and obturator internus (in the hip and pelvis); subscapularis (rotates the head of the humerus); and infraspinatus and teres minor (parts of the rotator cuff).

Although the investigators lacked historical imaging data on the volunteers, they reasoned that the muscles that are affected most frequently across the study population are those that must have been affected earlier in the disease process. The frequent involvement of the hamstring muscles in nearly all of the volunteers, for instance, suggests that the hamstrings are among the earliest muscles affected in FSHD. Yet knee flexion weakness, which one would expect to see as a result of hamstring weakness, is rarely an early clinical complaint. This is likely due to compensation by the remaining muscles in that muscle group.

Why is this important? It suggests that imaging of the hamstring muscles is an early indicator of disease progression, something that might not have been recognized based purely on clinical strength measurements.

Only a minority of muscles (three to 14 muscles per subject) were hyperintense (presumably because of edema) on STIR imaging. Over the entire study population, only 79 of 1,330 muscles fell into this classification. Although STIR hyperintensity was associated with all levels of fat infiltration, it was rarely seen in muscles with the highest fat infiltration. This observation supports a hypothesis that STIR hyperintensity reflects an inflammatory process associated with early stages of muscle degeneration.

Another part of this study that Leung said she finds interesting is the inclusion of asymptomatic individuals. "Several participants in this study did not have any muscle weakness but were found to have the mutation that causes FSHD through genetic testing that was done after a family member was diagnosed," she said. "In some of these individuals, we were able to find affected muscles on MRI, what we call subclinical (non-symptomatic) disease. Studying this population could give us valuable insight into factors that modify the severity of FSHD."

The ability to detect these subclinical changes in both symptomatic and asymptomatic individuals is a major advance toward clinical trial preparedness in FSHD.

"Although this study population has been extremely informative, it is still a very small study sample," Leung cautioned. "There is tremendous variability in the FSHD population, and a small study can't hope to capture that variability. A crucial next step in developing MRI as a tool for studying FSHD will be to scan a larger number of individuals over time. I also think that it will be very informative to target the earliest stages of disease by imaging newly symptomatic individuals in the pediatric and adolescent populations.

"In the future, studies in larger numbers of patients will be crucial for developing any imaging biomarker that we may propose to use in clinical trials. In our study we excluded non-ambulatory individuals and individuals who had scapular fixation surgery. Both groups represent more severe manifestations of FSHD and should be included in future studies."

Leung noted that this research wouldn't

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Have You Made a Gift?

HAVE YOU MADE A GIFT TO THE SOCIETY IN 2015?

Our Board of Directors has pledged $384,805 and challenges you to help match it. Make your tax-deductible gift by December 31, 2015, using the enclosed envelope. Or contribute online at *www.fshsociety.org.* Act today! Thank you!

EMPLOYER MATCHING GIFTS

If your employer offers you options for directing the company's funds to a charitable organization of your choice, please explore it. This is a great way to double, triple, or even quadruple your gift.

#FSHDStronger Campaign

Raising awareness one T-shirt at a time

by JUNE KINOSHITA

Our #FSHDStronger T-shirt campaign proved a hit with the FSHD community. "I like this a lot!!!" Maurice Atkinson posted on the FSH Society's Facebook page. "You know it's tough living with this thing, but I would bet I wouldn't have accomplished as much as I have in this life if I were well and not had FSHD. The physical limitations have made me focus on so many other things that have been satisfying."

The campaign ran for 21 days in August and September, and raised over $3,100 for the FSH Society.

"This T is wonderful," posted Deborah Schwartz. "We should keep this one in permanent stock."

We're happy to announce that the shirts, hoodie, and zip-front jacket continue to be available on our Teespring Store. If we reach a minimum number of orders, the shirts will go back into production.

You can order your shirts at *https://teespring.com/stores/FSHsociety.* FSH Watch

WHOLE-BODY MRI YIELDS NEW INSIGHTS

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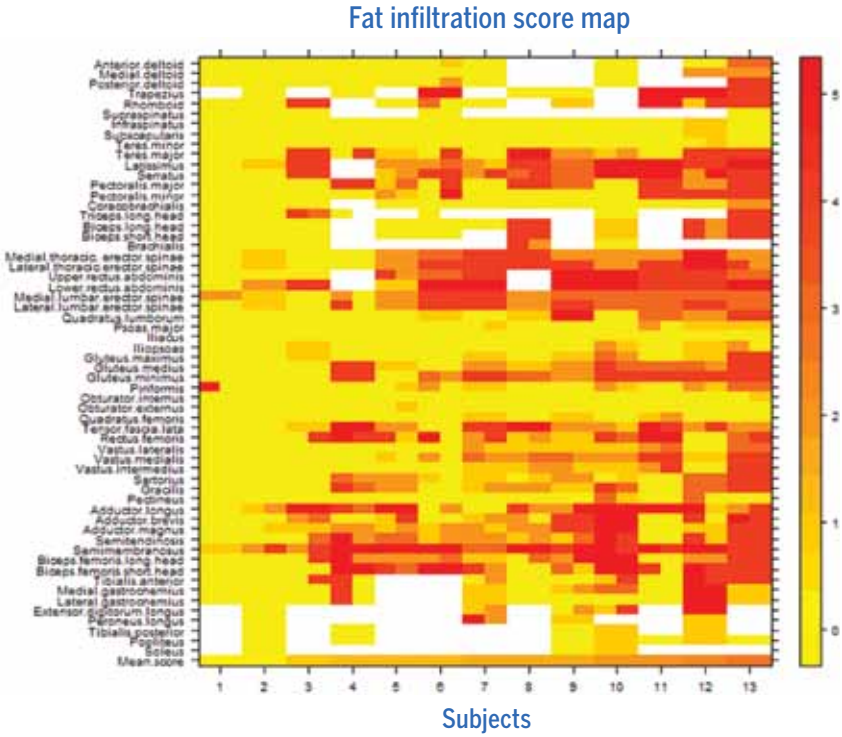
be possible without ongoing collaboration among radiologists, biomedical engineers, radiographic technicians, and clinicians in her own institution. "Maximizing the potential of MRI as a research tool will require studying patient populations at multiple locations, so we will need to collaborate with investigators at other institutions as well," she said.

Editor's note: Jim Fox wrote a great first-person account of participating in this research study in the Spring 2014 *FSH Watch.* The FSH Society supported this research through a grant award to the project called "Magnetic Resonance Imaging and Spectroscopy Biomarkers in FSHD." Investigators: Doris G. Leung, MD, and Kathryn R. Wagner, MD PhD, Hugo W. Moser Research Institute at Kennedy Krieger, Baltimore, Maryland. From August 2011: $100,550 over two years. FSH Watch



This chart shows a "heat map" of all 1,330 muscles from 13 individuals with FSHD. The subjects are arranged left to right from the lowest to highest average MRI score. The MRI scores represent the degree of fat infiltration, from least (0=yellow) to most (5=red). Higher fat (orange to red) indicates greater loss of muscle. The muscles studied are listed on the vertical axis (left) in order of their anatomic location, head to foot. Muscles on the left and right side of the body are placed to the left and right of the numbered tick mark for each individual. Figure reproduced with permission from *Muscle & Nerve.*

Reference

Leung DG, Carrino JA, Wagner KR, Jacobs MA. Whole-body magnetic resonance imaging evaluation of facioscapulohumeral muscular dystrophy. Muscle Nerve. 2015 Oct;52(4):512-20. doi: 10.1002/mus.24569. Epub 2015 Mar 31.