

FSH Watch

2014 Annual Research Report



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



FSHD is one of the most prevalent neuromuscular disorders

New Dutch study indicates many remain undiagnosed

by **JUNE KINOSHITA**
FSH Society

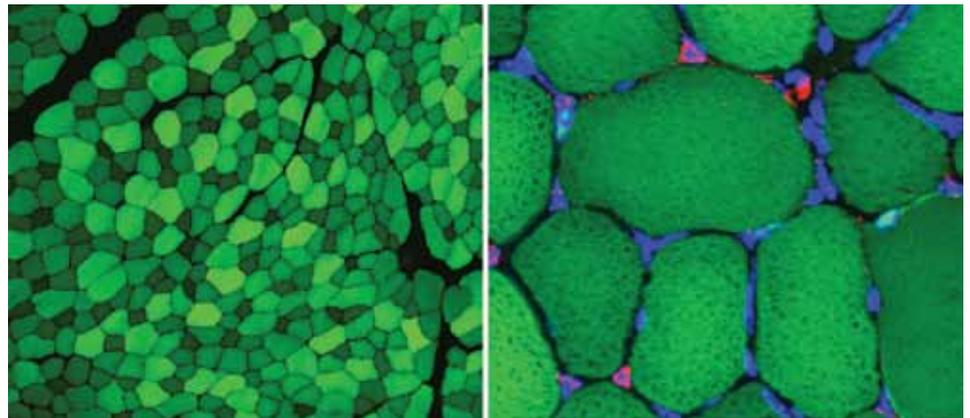
Many researchers have long suspected that the number of individuals with FSHD is significantly greater than has been reported. A new study from the Netherlands bears out this suspicion and finds that the prevalence of FSHD is 12 in 100,000 (or one in 8,333)—more than double the commonly cited figure of five in 100,000.

At the new rate, the worldwide population of people with FSHD stands at nearly 870,000, assuming that FSHD occurs at the same rate across all human groups. This is a big assumption and demands further investigation. That said,

... continued on page 23



A method used to estimate wildlife populations was employed to calculate FSHD prevalence.



Adeno-associated virus (AAV) is used to deliver new genes to mouse muscle cells. The green color (left photo) shows that the new gene was successfully delivered to all the muscle cells in the sample. In a magnified image (right), the light blue color reveals muscle stem cells. Dark blue colored objects are supporting cells in between muscle cells, while the red color highlights blood vessels and another type of stem cell. This AAV gene delivery method is being developed by the new NIH-funded Wellstone Muscular Dystrophy Center, Seattle, Washington, and could one day be used to deliver therapy for patients with muscular dystrophy.



New center to design therapies for muscular dystrophy

Goal is to bring promising lab treatments into patient trials

by **LEILA GRAY**
Seattle, Washington

A newly established muscular dystrophy research center in Seattle hopes to bring promising laboratory results into therapeutic trials. The center will design and test treatments for the most common forms of the muscle-wasting disorder Duchenne muscular dystrophy and FSHD.

Muscular dystrophy interferes with the growth and repair of skeletal muscle and causes progressive loss of physical ability. Movement and mobility decline, and lives can be cut short if breathing muscles fail. Because

there is no cure, treatment options for people with the disease have been limited.

Now, after years of scientific studies, several potential methods for managing the disease are on the horizon.

“Our plan is to develop a clinical infrastructure to advance cures for muscular dystrophy,” said Jeffrey S. Chamberlain, the McCaw Chair in Muscular Dystrophy and professor of neurology at the University of Washington. He co-directs the center with Stephen Tapscott, an investigator at the Fred Hutchinson Cancer Research Center and a University of Washington professor of neurology. Scientists and clinicians from their institutions will collaborate with those from Seattle Children’s and University of Rochester (NY).

... continued on page 23

WHAT'S INSIDE

page **5**
The gift my disability gave me

page **8**
New FSHD mouse has on-off switch for DUX4

page **9**
“Coming out” for a cause

page **16**
Toward Treatment Discovery



A remarkable year

Accomplishments that touch all our lives

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FSH Watch

SUMMER/FALL 2014

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Daniel Paul Perez

Dear Friends,
Over the past 23 years, the FSH Society has evolved into an effective, dynamic community of patients, families, and researchers working together to define our disease and understand its genetic basis. Now we are working to learn the biological processes driving this disease, and from there, how to treat it, and stop it. The FSH Society has endeavored to raise awareness of FSHD worldwide. Together we are succeeding. As you read this issue, I hope you will get a sense of the full scope and enormous success of our collective work.

We are still here advocating on your behalf, pushing hard to raise the level of research funding. On September 26, 2014, President Obama signed into law the MD-CARE Act Amendments. This new version of the MD-CARE Act will ensure that all muscular dystrophies continue to receive attention and funding by the federal government.

Thank you all for your efforts and outreach to your representatives in support of this vital legislation. A special thanks and shout out to our Washington counsel Morgan Downey, who conceived the initial idea of having the MD-CARE Act in 1999 and helped us pitch and introduce it to other muscular dystrophy nonprofits. It is the single most important piece of legislation impacting funding and progress in muscular dystrophy, fostering approximately \$500 million of investment in

research funding from the National Institutes of Health over the past 13 years. This is a monumental accomplishment and clearly speaks to the tight integration among all dystrophy nonprofits backing this effort.

The year 2013 was remarkable for progress on FSHD research, and 2014 is turning out to be even more so. With your generosity, the Society is investing heavily in cutting-edge research yielding high-quality results. In 2013, we funded \$661,585 in research grants. (This does not include the Society's additional support for research meetings, small grants, and travel awards for researchers and reimbursement of travel expenses for patients participating in research studies.) This year to date, the Society has funded \$802,715 for nine research grants.

We are most appreciative of Professor David Housman, chairman of the FSH Society Scientific Advisory Board (SAB), and his colleagues on the SAB, who have given of themselves and their knowledge, insights, and time, at no charge, year after year, to bring about discoveries into FSHD.

We're laying the foundations for clinical trials by collaborating with organizations from several countries to fund an FSHD clinical trials network of academic research centers working together in developing, testing, and validating clinical outcome measures and biomarkers.

The Society is also helping to build assets for clinical trial endpoints, trial measurements, natural history, biomarkers, and improved genetic testing. We are excited about the ongoing MRI (magnetic resonance imaging) work we've funded and the novel real-time effort to un-

It is our editorial policy to report on developments regarding FSHD, but we do not endorse any of the drugs, procedures, treatments, therapies, or products discussed. We urge you to consult your physician about any medical interventions.

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derstand the immunological process to identify biomarkers of disease activity to possibly develop a targeted therapy.

The Society's forté has been seed funding that leads the way to new discovery and possibilities. Our hope—my hope—is to have a very clear understanding of what causes FSHD, based on rigorous and reproducible data so that, ultimately, the effects of the disease can be stopped and even reversed. Projects, highlighted in this issue, aim to help lead to targeted treatments by understanding:

- DUX4 regulatory pathways;
- DUX4 expression/repression;
- epigenetic changes of the D4Z4 array by using regulatory targets of DUX4;
- how to perform gene editing using transcription activator-like effector nuclease (TALEN) and CRISPR/Cas9 technology to modify the FSHD locus and permanently inhibit DUX4 expression;
- how to promote the appropriate epigenetic repression of DUX4 using small molecules (drugs);
- the influence of protein-protein interactions on the DUX4-associated pathogenic cascade;
- if epigenetic silencing can be introduced by targeting D4Z4 with genomic engineered sequence-specific chromatin nucleators;
- DUX4's protein-binding partners and how elevated DUX4 causes FSHD;
- primary DUX4 transcriptional-mediated gene expression changes to help identify causal signaling events in FSHD;
- silencing of FAT1 and its role in pathogenesis of FSHD.

Big news! In mid-August, population-based estimates regarding FSHD individuals showing symptoms were revised based on updated Dutch data, indicating that FSHD may be one of the most prevalent neuromuscular disorders. The new study estimates that FSHD may affect one in 8,333 individuals worldwide, which is more than 860,000 people.

Our top priority is to generate an animal model we have confidence in that will be used for assessing the impact of an FSHD therapeutic. This has been a central effort of the Society's research program and investments. We are pleased to highlight in this issue the

work on the DUX4 mouse that we helped start in 2007 in Michael Kyba's lab while he was at University of Texas Southwestern, and the funding of some really interesting models under development at the University of Massachusetts by Peter Jones that should be a great help if all goes well. This effort will tie into our Critical Path initiatives and into trials, endpoints, and FDA issues. If you are interested in becoming a supporter of our Critical Path initiatives, please contact us.

This has been a remarkable year for research, with accomplishments that touch the lives of every FSHD patient in the world. Your generosity has helped the FSH Society fund some of the key research studies, which have generated continued progress in understanding FSHD.

And in August, in Boston, we had one of our most profoundly successful biennial FSHD Connect Patient-Researcher meetings. It was a truly remarkable meeting with 210 patients, researchers, clinicians, families, friends, funding agencies, and industry coming together for an interactive dialogue. This meeting is very much appreciated by both patients and researchers, and helps in every aspect of people's lives. Be sure to check out the talks and keynote speech from Senator Elizabeth Warren on YouTube. We'll have more on this stellar meeting in the next issue of *FSH Watch*.

Your contributions also enable us to serve patients and families affected by this disease with peer-to-peer counseling, face-to-face meetings, support groups, informative materials, and other resources.

We are most proud of having earned a Charity Navigator Four-Star rating for six consecutive years. This external measure helps us validate to you—our donors—that your dollars go where they are intended: toward finding a cure!

Please consider increasing your gift to the Society at this watershed moment. Thank you again for all of your support, for helping get the work done, and continued best wishes.

Sincerely,



Daniel Paul Perez
President & CEO

FSHD Muscle Biopsies Needed for Research Repositories

Muscle biopsies play a crucial role in FSHD research. A muscle biopsy is a surgical procedure in which a small sample of muscle is removed. The procedure is usually done as outpatient day surgery under local or general anesthetic.

FSHD clinicians and researchers need two types of biopsies, depending on the requirements of their work. A needle biopsy involves inserting a needle into the muscle to a certain depth and capturing the sample of muscle inside the needle. The incision is usually five millimeters deep and a few millimeters in length.

An open biopsy requires making an incision or a cut that is a few centimeters in length; a sample of muscle about the size of a pea is removed, and stitching is required to close the incision.

Please consider making a valuable gift to research by contacting Daniel Paul Perez at the FSH Society or emailing biopsy@fshsociety.org.



FSH Society grants

From the February 2014 Cycle

GRANT SUMMARIES CONTRIBUTED BY THE GRANT APPLICANTS.

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

Sujatha Jagannathan, PhD, and Stephen Tapscott, MD, PhD, Fred Hutchinson Cancer Research Center, Seattle, Washington

\$116,725 over two years. This grant has been named in memory of Dotty Lynch, wife of the FSH Society's Washington, DC, counsel Morgan Downey.

Summary: FSHD is a prevalent and currently untreatable myopathy caused by the misexpression of DUX4, a germline transcription factor, in post-mitotic muscle cells where it activates a germline transcription program and also induces expression of retro-elements and repetitive sequences. Ectopic expression of DUX4 triggers cell death in a variety of cells including primary myoblasts and immortalized epithelial cells via an unknown mechanism.

We recently discovered that DUX4 reduces the efficiency of a cytoprotective, RNA quality control pathway called the nonsense mediated RNA decay (NMD), thus stabilizing hundreds of aberrant RNAs. It is known that reduced NMD efficiency can affect cellular proteostasis due to expression of malformed proteins, which can in turn lead to cytotoxicity through the unfolded protein response (UPR). Hence, we hypothesized that DUX4-induced reduction in NMD efficiency leads to the stable expression and translation of aberrant RNAs, generating toxic proteins that cause cell death, possibly through UPR-mediated apoptosis.

In Aim 1, we will identify the mechanism by which DUX4 expression reduces NMD efficiency. In Aim 2, we will determine the contribution of reduced NMD to DUX4-induced cytotoxicity and elucidate the downstream mechanisms responsible for this phenomenon. These studies will provide valuable insights into the mechanism of DUX4-induced cytotoxicity and uncover potential novel avenues for therapeutic intervention for FSHD.

► **BET PROTEINS AS THERAPEUTIC TARGETS IN FSHD**

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

\$51,425 for one year. This grant has been named in honor of William G. Michael, long-time Treasurer of the FSH Society, on the occasion of his retirement.

Summary: Promoting the appropriate epigenetic repression of DUX4 is a therapeutic strategy for FSHD that addresses the underlying mechanism of disease pathology. However, the molecular details of DUX4 de-repression are not completely understood, and few specific targets amenable to small molecule drug intervention have been identified.

We have used a chemical genetics approach to identify a key role for the bromodomain and extraterminal domain (BET) proteins in the epigenetic switch that activates DUX4. The experiments proposed here will extend these findings by confirming by genetic means the specific BET family member(s) involved in pathogenic DUX4 expression. This will be accomplished by a combination of

RNAi technology and overexpression studies.

In addition, we will similarly determine the involvement of mediators of the BET pathway of transcriptional activation including the role of protein acetylation. We will also determine the functional effects of BET inhibitors (BETi) on FSHD muscle biology in vitro.

A 24-hour pulse of BETi results in a sustained decrease in expression of DUX4 and its downstream targets in cultured myotubes without long-term interference with muscle differentiation. These data demonstrate that the pharmacodynamics of DUX4 inhibition and undesirable effects on muscle cells are distinct. We propose to perform a more detailed analysis of the effects of BETi on FSHD myoblasts and myotubes by comprehensive gene expression and functional assays. In addition, we will assess protection of FSHD muscle cells from DUX4-induced apoptosis during myotube differentiation.

► **FSHD CLINICAL TRIALS NETWORK WORKSHOP**

Rabi Tawil, MD, University of Rochester Medical Center and Fields Center, New York

\$25,000 for one meeting planned for March 2015

Summary: The discovery of a unifying hypothesis for the cause of FSHD means that, for the first time since the discovery of the genetic defect 20 years ago, it is possible to develop targeted treatments for FSHD. The next steps on the road to therapeutic development are: preclinical work to develop and test potential treatments, and the conduct of clinical trials to determine the efficacy of such treatments. A number of laboratories are actively investigating various therapeutic approaches to treat FSHD. In parallel to this research, it is vital that clinical investigators work to develop the tools necessary for the efficient conduct of future FSHD clinical trials.

Successful clinical trials depend on several factors including: access to patients, a good understanding of the natural history of the disease, and reliable outcome measures that are sensitive to change. Optimal, accepted standard outcome measures will result in more effective and efficient clinical trials, significantly shorten the drug development process, and result in more robust clinical trial data.

The trial preparedness workshop recently held in Leiden [in April 2013] developed and published a consensus approach to what is needed for clinical trial readiness for FSHD and sets forth the milestones necessary to accomplish this objective.

The development and validation of outcome measures require a prospective, longitudinal study with a substantial number of patients followed for at least one year. To achieve this goal it is important to coordinate the development and validation of clinical trial tools across multiple centers.

To this end, this proposal seeks to establish an FSHD Clinical

... continued on page 5



The gift my disability gave me

FSHD opened my eyes

by **TRISHA LYNN SPRAYBERRY**

Aloha, Oregon

We all have our ups and downs. But the extra burden of experiencing a disability like FSH muscular dystrophy could appear to be a challenge too daunting to fathom, let alone one that has any positive aspect to it.

FSHD is a progressive, inherited genetic disease. That means that over time, the disease will get worse. The muscles weaken and atrophy more and more over time, leading to the inability to run, or to raise your arms above your head. Eventually, you may lose your ability to walk and may require a wheelchair. And then, if you don't first succumb to an illness or complication, you may become dependent on others for everything as your body weakens and the muscles wither away.

Such a future sounds so bleak when it's put that way. But it's a matter of perspective—an unfortunate one that lies at the basis of the stereotypes that envelop those of us who do suffer from this disease. It's no wonder why it's hard for people who are unfamiliar with FSHD to see beyond this narrow and negative view.

Most people won't know what I have just from glancing at me in public, or what FSHD is if they were to ask me. What they see is a woman in a wheelchair. And all too often, it's a short leap from that wheelchair to making a judgment about who I am.

I'm going to tell you why my diagnosis, and all that it encompasses, was the best thing to happen to me.

I have to confess that I was a different person before my symptoms began to really affect my abilities. I was a cocky, shallow, image-obsessed person always looking in the mirror, fixing my make-up, who was embarrassed by my disabled family members. My mom, all of her siblings, and her mother—my grandmother—all were diagnosed with FSHD.

Even though I knew since a young age that I also had this devastating disease, I didn't have any symptoms at the time, so I felt that FSHD just wouldn't happen to me in the same way. It



FSHD strikes three generations. Clockwise from top: Trisha Sprayberry's daughter Adara Petersen, Trisha Sprayberry, her nephew Noah Bradshaw and mother Terese Kleve.

wasn't until my disease manifested in my physical appearance that the reality of my diagnosis sank in for me.

It opened my eyes. And the change in my attitude was almost instantaneous.

It tore down my prejudgments, prejudices, my stereotyping, and preconditioned thinking—not only in how I view others, but also of the world around me. My whole mindset completely changed.

I was no longer seeing people through the lens of shallow judgments and obsessions with image or privilege that seem to be mainstream thinking these days.

As though a blindfold had been removed, I began to see people and the world beyond surface appearances. I was brought in touch with my own humanity and mortality. I was given the gifts of empathy and compassion for others. I was given the gift of knowledge of our purpose to care for humanity, especially for those who might be vulnerable and suffering, and in need of a little help beyond their own ability. I was given the vision to see beyond the flaws of the human condition and to advocate for an equal life experience for those with disabilities.

Sometimes the only way we are able to change our perspective is because our perspective is changed for us. Too many people have this thought in their heads that nothing “bad” will ever happen to them. This is just a defense mechanism our minds deploy to protect us from negative thoughts.

We avoid unpleasant thoughts. We do the same thing to people. When we see people who are disabled, we also avoid them. Unfortunately for those of us who happen to be disabled, we do not have the luxury of just avoiding our disabilities. We also do not have the luxury for others to avoid us.

We need more people to open their eyes. We need more people to advocate not just for our disabilities and needs, but even more for our abilities and what we can contribute if we can gain a foothold into independence and the world we are supposed to share. Promote and support us as people, not as a diagnosis, and what we can achieve if given the opportunity and proper tools and equipment. **FSHWatch**

Adapted from: *The Huffington Post*. Original source link: http://www.huffingtonpost.com/trisha-lynn-sprayberry/the-gift-my-disability-gave-me_b_4912682.html

FSH SOCIETY GRANTS

... from page 4

Trials Network. This network will be composed of academic research centers working collaboratively in developing, testing, and validating clinical outcome measures and biomarkers. Establishing and validating a consensus for compatible outcome measures and biomarker assessment, both molecular and radiological, among network members are necessary for future multi-institutional FSHD

therapeutic trials, and, just as important, for comparison of trials performed at different institutions.

The existence of such a network significantly increases the likelihood that promising therapeutic interventions in FSHD come to clinical trials and that those trials will have a transparently meaningful outcome. **FSHWatch**

2014 FSHD International Research Consortium

Fifteen organizations strong

by JUNE KINOSHITA

The 2014 FSH Society FSHD International Research Consortium workshop for research and clinical professionals met at the San Diego Marriott and Marina Hotel on Friday, October 17, through Saturday, October 18, noon. Friday was a full-day workshop, and Saturday was half a day of research planning. The meeting is an ancillary meeting of the American Society of Human Genetics (ASHG) and was held prior to the opening of the annual ASHG conference in San Diego, California.

Co-chairing the meeting were:

- David E. Housman, PhD, from M.I.T. in Cambridge, Massachusetts, and chair of the FSH Society Scientific Advisory Board;
- Michael Altherr, PhD, from the Los Alamos National Laboratory, New Mexico, and FSH Society Scientific Advisory Board member;
- Stephen Tapscott, MD, PhD, from the Fred Hutchinson Cancer Research Center in Seattle, Washington, and co-director of NIH Wellstone Center for Cooperative Research on Muscular Dystrophy;
- Silvere van der Maarel, PhD, from the Leiden University Medical Center in the Netherlands and co-director of the Fields Center for FSHD Research at the University of Rochester.

Daniel Paul Perez, President & CEO of the FSH Society, served as organizational chair.



San Diego, California

Please contact Daniel Paul Perez for further information at 781-301-6650 or daniel.perez@fshsociety.org. This year's meeting featured many exciting advances in research. We will be reporting on the highlights in the next issue of *FSH Watch*. 

Scott Harper receives award

RECOGNITION FOR GENE THERAPY WORK

Scott Q. Harper, PhD, an FSH Society grant recipient, was named a 2014 Outstanding New Investigator by the American Society of Gene and Cell Therapy (ASGCT). He was one of four awardees recognized at the ASGCT 17th Annual Meeting in Washington, DC, and gave a talk on "Translating Facioscapulohumeral Muscular Dystrophy (FSHD)," which introduced thousands of attendees to the exciting progress in FSHD research.

FSH Society supporters can take pride in knowing that the Society encouraged Harper early in his career to begin this work and that their donations contributed to the research that was recognized by this award.

Harper's lab has been developing gene therapies for FSHD and other inherited myopathies using "RNA interference" (RNAi) technology. In addition, his lab is investigating the molecular mechanisms giving rise to FSHD and generating new animal models of the disease.

Early in his career, Harper made important contributions to gene therapy in Duchenne muscular dystrophy and Huntington's disease. Upon starting his own laboratory at Ohio State University in 2007, Harper began a program to



Scott Q. Harper, PhD

develop RNAi-based gene therapies targeting two diseases in particular: FSHD and limb girdle muscular dystrophy 1A (LGMD1A).

In the summary of his ASGCT lecture, Harper writes: "...I consider my lab's best paper to date our *Annals of Neurology* paper describing a ... basic study that served as a springboard for all future FSHD work in my lab and was impactful to the FSHD field, having been cited 47 times since April 2011. In this paper we: (1) established an AAV (adeno-associated virus)-based mouse model for FSHD (which was lacking in the field); (2) demonstrated that the FSHD candidate gene, DUX4, was toxic to muscle and the mechanism of toxicity involved its ability to (3) bind DNA and (4) stimulate apoptosis through activation of p53.

"We subsequently used this model to demonstrate proof-of-principle for a potential RNAi therapy of FSHD targeting DUX4 (in a follow-up *Molecular Therapy* paper). In addition, I am happy that our p53 findings have now been replicated by others in the field, and that the 'reverse gene therapy' approach we employed in this study (i.e., delivering a toxic gene to muscle with AAV instead of a therapeutic) provided essential data we used to acquire funding for creation of a stable line of transgenic/knock-in mice containing the human DUX4 gene, which will ultimately be useful to the FSHD field and our lab, as we continue developing therapeutic approaches for FSHD, targeting DUX4."



#FSHDselfies

Shoot a selfie, raise awareness

SHIFT COMMUNICATIONS
Newton, Massachusetts

selfie noun, informal (also selfy; plural selfies): a photograph that one has taken of oneself, typically one taken with a smartphone or webcam and uploaded to a social media website—*Oxford English Dictionary*

In July, the FSH Society launched a major national social media campaign to raise awareness about FSHD. Actor Max Adler, of *Glee* and ABC Family's *Switched at Birth*, helped us kick it off with an editorial in *The Huffington Post*. Max's mother and grandmother were affected by the disease, and he has been one of the most vocal celebrity advocates for FSHD.

The ever popular social meme of the selfie is considered rather narcissistic, but we're taking the term and making it into a positive force to raise awareness about FSHD. As you know, many people affected by FSHD are unable to smile, and that's where the impetus for the campaign started.

We want to share selfies of those affected by FSHD smiling and not smiling (or smiling on the inside) and give others a chance to smile for us and share these faces—the whole array of them—on Facebook, Twitter, and Instagram.

A generous donor has pledged \$1 for every selfie posted, up to \$5,000. We are getting close, with more than 3,500 selfies posted as of early October. Please help us reach our goal!

Here's how to get involved:

- Take a selfie with your smartphone.
- Write a tweet or post using the hashtag #FSHDselfies (see sample tweets below).
- Post it publicly on Facebook, Twitter, or Instagram.
- Encourage your friends and colleagues to do the same.

The goal of the campaign is to get folks talking about FSHD and drive those who don't know what it is to find out and spread the word to others.

Please make sure to connect with us via Twitter and Facebook and join our #FSHDselfies campaign today! Help us reach our goal of 5,000 #FSHDselfies!

Sample tweets:

- Proud to share my first selfie for #FSHDselfies to raise awareness for the incurable disease #FSHD and the @fshsociety. [insert selfie]
- Can you smile? Some with #FSHD can't. Smile for #FSHDselfies and help the @fshsociety raise awareness for #FSHD. [insert selfie]
- Do you know what #FSHD is? Post a selfie with #FSHDselfies to spread the word about this rare, incurable disease. [insert selfie]
- My [friend or family member] is affected by #FSHD. Help me raise awareness for this rare, incurable disease with #FSHDselfies and @fshsociety.
- On [insert date] I was diagnosed with #FSHD. Help the @fshsociety raise awareness and find a cure by sharing a selfie. #FSHDselfies 



FSHD Champions

CONNECTING AND COMMUNICATING ON FSHD

FSHD Champions is an informal, international group consisting of FSHD advocacy and research funding organizations working together since 2012 to promote collaboration and transparency in FSHD research. Core members are: Chris Carrino Foundation, Friends of FSH Research, FSHD Canada, FSHD Europe, FSHD Global Research Ltd., FSHD Stichting, FSH Society, and Shaw Fischer families. Allied organizations that also fund FSHD research include: Association Française contre les Myopathies (AFM), Muscular Dystrophy Association (MDA), MD Campaign (UK), MD Canada, U.S. National Institutes of Health (NIH), Prinses Beatrix Fund, and Vereniging Spierziekten Nederland (Netherlands Neuromuscular Diseases Association—VSN).

Since the initial meeting, the FSHD Champions Working Group has convened monthly by webinar and is making progress on a number of fronts, including:

- compiling data on worldwide funding of FSHD research;
- surveying member organizations on research priorities;
- funding travel grants to promote FSHD research;
- promoting FSHD research funding and resources at scientific meetings;
- collaborating on awareness-raising campaigns.

This year's FSHD Champions in-person meeting was held on October 18, 2014, in San Diego, California, the day after the FSHD International Research Consortium meeting. Members from each organization's executive staff and Board of Directors attended to discuss how to achieve faster progress by working more closely together. Kees van der Graaf of FSHD Stichting and Daniel Paul Perez of the FSH Society were the co-conveners of the meeting.



New FSHD mouse has on-off switch for DUX4

Will help probe DUX4 toxicity and test therapies

from THE UNIVERSITY OF MINNESOTA
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Researchers at the University of Minnesota have developed an animal research model for FSHD to be used for muscle regeneration research as well as studies of the effectiveness of potential therapies for FSHD.



Michael Kyba, PhD

The research is published in the August 27, 2014, issue of the journal *Cell Reports*.

There is no treatment for FSHD, which is thought by many to be the most common type of muscular dystrophy. FSHD is an unusual genetic disorder because, unlike most genetic diseases, it is not caused by the loss of a functional gene, but rather by the modification of an existing gene, through a genetic mutation. This mutation makes the gene more active, so patients with FSHD express a protein, named DUX4, which interferes in an unknown way with muscle maintenance.

“We felt that an animal model would advance progress toward a cure for FSHD for two reasons,” said Michael Kyba, PhD, lead researcher and associate professor in the Medical School at the University of Minnesota. “First, it would allow us to understand what DUX4 does in muscle to cause muscle loss, and second, it would provide a system in which efficacy of potential therapies could be evaluated before they are tested in humans.”

The mouse model designed by Kyba and his team allows the disease-associated DUX4 protein to be produced when mice are treated with doxycycline, an antibiotic. The amount of DUX4 can be controlled by varying the dose of doxycycline. Researchers expected the mice to be normal until they were treated with doxycycline; however, even when DUX4 was in the “off” state, mice showed profound disease effects, some related to FSHD as well as additional effects not seen in FSHD patients.

“Nothing is black and white in biology,” says Kyba. “No gene is truly off, and the off

state in this case resulted in enough leaky DUX4 expression to kill the mice.”

The team solved this problem by moving the gene to the X chromosome. Because females have two X chromosomes, only one of which is actively used in each cell, the female mice were healthy enough to enable the DUX4 mice to reproduce even though all of their male progeny with the DUX4 gene died. The fact that multiple levels of turning off the DUX4 gene were necessary to allow mice to survive showed that DUX4 is more toxic than researchers expected.

“We learned a lot with this animal model, but perhaps the most important finding was what we observed when we transplanted skeletal muscle stem cells,” said Kyba.

The team could isolate muscle stem cells from the male mice before they died, and when they transplanted them into muscle-damaged recipient mice, they found that the stem cells were able to regenerate new muscle. But when even low doses of doxycycline were given to the recipients to turn on DUX4 in the skeletal muscle stem cells, muscle regeneration was severely impaired. This suggested that a defect in skeletal muscle regeneration may contribute to muscle loss in FSHD. The finding also provides a very sensitive



Mice genetically engineered with the DUX4 gene show that extremely low levels of DUX4 are highly pathological. Mice carrying the gene are runted and display a number of other problems, some of which are related to FSHD, such as retinal vascular changes, and others that are of unknown relevance, such as a skin pathology that results in hair loss. Most such mice only survive to about six weeks of age.

quantitative readout of DUX4 activity.

“This assay, in which we count new muscle fibers produced by transplanted DUX4-expressing muscle stem cells, will be very useful in testing therapeutics,” says Kyba. “Drugs that target DUX4 should allow these transplanted DUX4-expressing muscle stem cells to make more new muscle fibers.”

As researchers develop drugs that target the DUX4 protein, the hope is that these mice will be used to determine whether such drugs can reach skeletal muscle and allow muscle damage to be repaired, even in the presence of DUX4.

Support for the project was generously provided by the Dr. Bob and Jean Smith Foundation, the Friends of FSH Research, and the FSH Society.

This research was also supported through grants from the National Institutes of Health, both for the project and individual researchers, numbers R01 AR055685, P30 AR0507220, R01 AR055299, U01 HL100407, T32 AR07612, K02 AG036827, R01 HL68802, R01 HL103773, and R01 HD053889. [FSH Watch](#)

Editor's note: Dr. Kyba and colleagues used a gene-engineering tool known as “the doxycycline-inducible system.” They created an artificial gene that contains both a doxycycline switch (taken from bacteria that are resistant to doxycycline) and the DUX4 gene (taken from the human genome). Because this artificial gene has the doxycycline switch, they were able to turn on DUX4 with doxycycline. But doxycycline only has this effect on the artificial bacterial/human gene in the genetically modified mice. Doxycycline has no effect on the human DUX4 gene, because the human DUX4 gene lacks the bacterial doxycycline switch.

Reference

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SAN FRANCISCO SERENADE

Some 200 guests were treated to a stellar evening of music on July 24 at “Songs in the Key of Steven Blier,” the first annual San Francisco Bay Area benefit event for the FSH Society. Held at the famous jazz club Yoshi’s, the evening began with a silent auction and reception featuring Michelin-rated, Asian-inspired hors d’oeuvres and a selection of California wines. Auctioneer Liam Mayclem, an Emmy-winning television host, entertained the crowd spiritedly while artfully encouraging higher bids during the live auction. The main event of the evening was a joyous, magnificent performance by opera legend Frederica von Stade and acclaimed pianist Steven Blier. They were joined by María Valdés and Efrain Solis, who added their own vocal fireworks. The repertoire ranged from Cole Porter to Broadway show tunes to Argentinian and Cuban ballads to opera. The evening netted over \$75,000 for the FSH Society Research and Education Fund. East Coast supporters of the FSH Society enjoyed more musical magic from Steven Blier at the September 29 “Festive Evening of Song” in Tarrytown, New York.



Frederica von Stade

LAKE PARTY MAKES A SPLASH!



On July 5 we held our second annual FSHD fundraiser at Gull Lake, Michigan, attended by 210 enthusiastic partygoers. Our intention was to raise awareness and funds within a convivial atmosphere amongst community, friends, and family. Our daughter Jess catered the event, longtime friends Mark and Jim encouraged spirited bidding, and the sunset provided a stunning backdrop across the lake! Family and friends worked furiously with volunteers from a local school to ensure a spectacular evening.

—Michelle Mackay

“Coming out” for a cause

The #FSHDselfies campaign

by KELLY MAHON
Arlington, Virginia

My hands were shaking and my stomach was doing somersaults. You can do it, the voice in my head said. I was absolutely terrified.

When I hit “post” on my first-ever selfie in honor of the FSH Society’s awareness and fundraising campaign, #FSHDselfies, my anxiety only heightened. Then my photo got a like. Then another. Then another. I couldn’t keep up with the activity and comments.

By lunchtime, dozens of my friends had posted their own selfies to social media. By dinner-time, there were hundreds. From elementary school friends to high school and college classmates, to former neighbors, the CEO of my former employer, and even friends of friends I have never met posted selfies and words of support for me. I definitely found out what it feels like to “go viral”!

Like many of us with FSHD, I avoid having my photo taken. In fact, the worst day of the year growing up was always class picture day. My inability to flash a toothy smile has caused me to face inevitable questions every time someone whips out a camera. Why don’t you smile? Why so serious? Why are you never happy?

By participating in the selfie campaign, I was finally responding to all of those well-intentioned but deeply hurtful questions in a positive way. And you know what? It felt amazing.

Before the FSH Society’s campaign, the only people who knew about my FSHD diagnosis were family members and a handful of close friends. But I knew I could not let the opportunity to raise awareness and money for research pass by. I reasoned that there never would be a better time to “come out.”

I won’t lie. Posting that selfie was the scariest thing I have done in recent memory. I am a private person, generally not one for selfies, let alone sharing personal medical information on social media.

But, looking back, I am certain that coming out was the best decision I will make all year. I was instantly received with a world of support, even from places I did not expect. The selfie campaign helped me realize that there is strength in weakness and beauty in challenge. The overwhelming response showed me that I will never face this disease alone.

To my incredible support system: thank you. And to people living with the secret of their diagnosis, I hope you, too, will consider coming out. Participating in the #FSHDselfies campaign was nothing short of life changing in how I view my support system ... it’s bigger, warmer, and more accepting than I ever knew.

FSHD gives us many burdens to carry. Only when you share your story will others know to help you lighten the load. More importantly, though, you’ll feel like a weight has been lifted. Even though the campaign is nearing completion, there’s never a bad time to raise awareness. Go ahead—post that selfie! [FSHWatch](#)



Kelly Mahon and her pup thank friends for #FSHDselfies.

Editor’s note: See our story on page 7 for instructions on how to post a selfie.



BASIC SCIENCE AWARDS

Solving FSHD requires an understanding of disease mechanisms

by **JUNE KINOSHITA**
FSH Society

If most FSHD researchers today agree that DUX4 plays a central role in the disease, why is it important to continue to fund basic science to expand our understanding of disease mechanisms? Shouldn't all resources be aimed at DUX4 as the target for treating FSHD?

While we all hope that a method to knock down DUX4 will lead to a cure, we cannot, therefore, stop investigating other strategies. Unanticipated obstacles could prevent the use of anti-DUX4 genetic engineering technologies in actual patients. These methods might not reach all the muscles that need to be treated, or they could prove far too costly or have severe side effects. Stopping DUX4 may not be sufficient to halt or reverse disease processes that are already far advanced by the time patients present themselves for treatment. Or, there might be another key disease process that could be stopped by an inexpensive and safe pill.

The landscape of pharmaceutical research is cratered with costly failures. As leading ideas move into the drug development phase, the FSH Society maintains a strong commitment to ensuring that new ideas are being investigated, and that the pipeline for future treatments will not run dry.

▶ RESTORING GENE REPRESSION AT FSHD LOCUS

Perspective by **Valentina Casà, PhD student**

Grant title: Role of Polycomb Group Proteins in Facioscapulohumeral Dystrophy

Investigators: Valentina Casà, MS, and Davide Gabellini, PhD, Division of Regenerative Medicine, San Raffaele Scientific Institute and Università Vita Salute San Raffaele, Milan, Italy

From August 2012: \$45,000 over 18 months

Since I joined the group led by Davide Gabellini at San Raffaele Scientific Institute in Milan, I've been involved in the important task of linking the genetic defect of FSHD to its epigenetic alterations. In fact, different aspects of the disease suggest that genetics is not sufficient to explain why individuals develop FSHD, and the interplay between genetics and epigenetics is probably at the basis of FSHD. Epigenetics refers to all heritable changes in gene function that occur without changes in DNA sequence. In particular, I am involved in deepening the role of epigenetic factors called Polycomb, which mediate gene repression in crucial cellular processes.

Importantly, I discovered that Polycomb proteins are involved



Valentina Casà, PhD student

in gene repression at the FSHD locus. My work suggests that each D4Z4 repeat encodes for the specific recruitment of these epigenetic factors which are able to establish and maintain gene repression. Hence, the genetic loss of D4Z4 repeats taking place in FSHD could be linked to the epigenetic loss of Polycomb binding to the locus.

Both epigenetics and genetics are heritable, but only epigenetics is reversible. Hence, the epigenetic alterations at the basis of FSHD are important targets of therapeutic approaches for FSHD, and the characterization of these targets represents the ultimate goal of our work in Dr. Gabellini's lab.

▶ INTERACTIONS OF DUX4 WITH OTHER PROTEINS IS A KEY TO DEVELOPING INTERVENTIONS

Perspective by **Jocelyn Eidahl, PhD**

Grant title: Protein Chemistry and Protein-Protein Interactions of DUX4
Investigator: Jocelyn Eidahl, PhD, The Research Institute at Nationwide Children's Hospital, Columbus, Ohio

From August 2013: \$70,000 over one year

The DUX4 protein is widely accepted as the biological molecule that causes muscle damage in people with FSHD. Our lab is dedicated to studying the protein chemistry of DUX4. We know that two regions of the DUX4 protein play key roles in causing muscle damage, and both regions are needed to cause FSHD. The role of one of these regions is currently unknown, and our lab is working on understanding how it is involved in FSHD progression. We believe this region of the DUX4 protein could be interacting with other proteins that influence the ability of DUX4 to cause damage to muscles.

Our lab has already identified a number of candidates able to associate with the DUX4 protein, and our proposed research plan is to focus on how and why these interactions exist. If we determine that DUX4 is working with a protein that affects disease severity, we can then begin to develop therapies to prevent the proteins from interacting and thus prevent the muscle damage from occurring. We believe details regarding the physical interaction between DUX4 and other proteins are necessary for successful FSHD drug development. We are hopeful that our research will uncover important insights about the role of DUX4 in muscle dam-



Harper lab

age and help aid in developing treatments for FSHD.

► **EPIGENETIC MECHANISMS THAT REGULATE DUX4**

Perspective by Richard J. L. F. Lemmers, PhD

Grant title: Identification of the Epigenetic Mechanisms That Regulate DUX4 Activity in Skeletal Muscle

Investigators: Richard J.L.F. Lemmers, PhD, and Silvère van der Maarel, PhD, Leiden University Medical Center (LUMC) Department of Human Genetics, Netherlands

From August 2011: \$80,000 over two years; an FSH Society Marjorie Bronfman research grant

D4Z4 repeat array chromatin relaxation and transcriptional de-repression of the non-polyadenylated double homeobox 4 (DUX4) gene unifies D4Z4 contraction-dependent FSHD1 and contraction-independent FSHD2. Only from FSHD-permissive genetic backgrounds the DUX4 transcript originating from the most telomeric unit of the array can be stabilized by a polyadenylation (polyA) signal outside the array. Non-permissive chromosomes fail to stabilize DUX4 in the absence of this polyA signal. Somatic DUX4 de-repression in FSHD1 and FSHD2 leads to bursts of DUX4 protein in sporadic nuclei of cultured FSHD myotubes. DUX4 is highly expressed in the germline. It is low expressed in embryonic stem cells, and it subsequently gets silenced during differentiation. FSHD iPS cells fail to silence DUX4 during differentiation.

The regulatory mechanisms that act upon DUX4 in muscle are largely unknown, and currently we do not know how a protein that is expressed in minute amounts causes chronic and progressive muscle wasting. While others have used conventional overexpression vectors to study the effect of DUX4, we have consistently observed that using constructs in which the genomic organization of DUX4 is retained, i.e., within the context of D4Z4, the locus creates sporadic bursts of DUX4 expression: not only in FSHD1 and FSHD2 cultured muscle cells, but also in muscle cells cultured from our transgenic L42 mice and in C2C12 cells stably transfected with a genomic D4Z4 construct. These bursts already



Richard J.L.F. Lemmers, PhD

occur at low frequency in proliferating cells and increase in frequency during differentiation.

I aim to identify the epigenetic mechanisms that regulate the bursts of DUX4 activity. I will develop reporter constructs in which the DUX4 ORF in D4Z4 is replaced by a reporter gene but in which otherwise the genomic integrity of the distal DUX4 gene is preserved. These reporter constructs will be used in the following set of experiments:

1. Fluorescent reporter constructs will be used in life cell imaging studies to precisely characterize the bursts of expression. Although the highest somatic expression of DUX4 is observed in differentiated myotubes, occasional nuclei expressing DUX4 can also be observed during proliferation. Life cell experiments will establish whether bursts of DUX4 are cell cycle dependent or whether other factors regulate DUX4 expression. They will also establish whether a single nucleus can repeatedly express DUX4 or whether this is a one-time event.
2. Inserting a fluorescent reporter in the construct allows for the separation of expressing muscle cells by FACS sorting and comparison of the chromatin structure of expressing and non-expressing cells by ChIP with a panel of histone modifications that allows for the recognition of the major chromatin states in mammalian cells. These chromatin studies will be validated in our extensive panel of primary muscle cells of FSHD patients and controls. I expect this study to yield a comprehensive epigenetic map of the FSHD locus in DUX4 expressing and non-expressing cells.
3. The reporter construct will also be used in dedicated and in large-scale screens for compounds that activate or repress DUX4. I will use an established RNA-interference (RNAi) screen (collaboration with Dr. Agami, NKI, Amsterdam) to identify chromatin modifiers that affect the D4Z4 chromatin

... continued on page 12



BASIC SCIENCE AWARDS

... from page 11

structure. I will validate these studies in primary muscle cells of FSHD patients and controls. I expect this study to provide mechanistic insight into the chromatin structuring of the FSHD locus in patients and controls.

Currently, we have identified a uniform molecular mechanism for FSHD. I expect this study to contribute to the current gap in our model of how a protein that is expressed in minute amounts causes a progressive muscle disease.

► LOWER AUTOPHAGY ACTIVITIES IN FSHD

Perspective by Sachchida Pandey, PhD

Grant title: **Autophagy Defects in FSHD**

Investigator: **Sachchida Pandey, PhD, Children's Research Institute, Washington, DC**

From August 2012: **\$99,599 over two years**

Autophagy is a cellular process that cleans up damaged or unwanted materials in our cells. Too much autophagy activities in cells have been associated with many diseases. In skeletal muscles, an excessive amount of autophagy causes muscle wasting. On the other hand, a basic level of autophagy activity is required to keep our muscles in a healthy state. Insufficient autophagy activity also causes diseases such as collagen VI myopathy.

When examining muscle cells from individuals with FSHD, we discovered that the autophagy activities were lower in these cells compared to the cells from healthy siblings. The evidence includes lower expression of several proteins that are involved in forming autophagosomes, which are organelles performing the autophagy process, as well as lower numbers of lysosomes, which are organelles containing enzymes to digest the unwanted proteins in the autophagosomes. We are currently investigating the mechanisms of the differences observed and determining whether correcting the differences will be beneficial to individuals with FSHD.

► SHEDDING LIGHT ON INFANTILE-ONSET FSHD

Perspective by Zoë Sund

Grant title: **A Multicenter Collaborative Study on the Clinical Features, Expression Profiling, and Quality of Life of Pediatric Facioscapulohumeral Muscular Dystrophy**

Investigator: **Jean Mah, MD, Alberta Children's Hospital, Calgary, Canada**

From August 2010: **\$96,669 over two years; \$51,434 year 1, \$45,235 year 2. Project is being co-funded by the Muscular Dystrophy Canada FSHD Funds**



Jean Mah, MD

The primary objective of this study is to establish a common method to test muscles in individuals with infantile-onset FSHD. This study also looks at how infantile-onset FSHD affects other parts of the body and how it affects quality of life

for people living with this health condition.

Study volunteers will receive a clinical evaluation and cognitive, hearing, eye, and speech assessments. In addition, there are health-related quality of life questionnaires and an optional blood draw. By participating, FSHD patients are gaining the opportunity to learn more about their health. In addition, knowledge gained through this study may provide benefit to current and future FSHD patients.

We expect to complete enrollment of 50 participants by the end of October 2014. The study will not be taking on any additional participants at this point, but if you are a qualified individual and would like to be included in any future extension of the study, please contact Lauren Hache at LHache@childrensnational.org.

► MAPPING CHANGES IN MUSCLE FORMATION IN FSHD

Perspective by Peter Zammit, PhD

Grant title: **Dynamic Mapping of Perturbed Signaling Underlying FSHD**

Investigator: **Peter S. Zammit, PhD, King's College London, England**

From August 2013: **\$137,798 over one year to 18 months**

During muscle repair, muscle cells (myoblasts) multiply and then either fuse with damaged muscle fibers to heal them or fuse together to form new muscle fibers. This process is disrupted in FSHD, resulting in muscle fibers that are either thinner, or less well organized, than their healthy counterparts. This



Chris Bannerjee in Peter Zammit's laboratory.

Volunteers for research

Great news!

The international infantile-onset FSHD study expects to have completed enrollment by late October. The study will not be taking on any additional participants at this point, but if you are a qualified individual and would like to be included in any future extension of the study, please contact Lauren Hache at:

LHache@childrensnational.org



repair defect likely contributes to the major FSHD clinical symptoms of muscle weakness and wasting. Thus, understanding why repair is perturbed will allow us to suggest therapies that may be effective for restoring healthy muscle function in FSHD.

Our project started in May 2014 and entails stimulating healthy and FSHD patient myoblasts to turn into muscle fibers in the lab, and then taking samples through the process. We will then use state-of-the-art technology to measure changes in global gene expression during muscle fiber formation. This information will be analyzed using a sophisticated and powerful mathematical tool (algorithm) that we have developed to create a map of the signaling pathways during muscle formation in healthy and FSHD myoblasts to detect which pathways are perturbed in FSHD. We hope to then identify potential drug targets to improve muscle repair in FSHD. We are extremely excited about the potential of our project for understanding and treating FSHD.

► IS FAT1 NEEDED FOR MUSCLE REGENERATION?

Perspective by Angela K. Zimmermann, PhD

Grant title: **Specific Silencing of FAT1: Role in Pathogenesis of FSHD**

Investigator: **Angela K. Zimmermann, PhD, Centre National de la Recherche Scientifique, IBDML—Development Biology Institute of Marseille, Campus de Luminy, France**

From August 2012: **\$140,000 over two years**

The laboratory of Françoise Helmbacher studies the role of the FAT1 gene in facioscapulohumeral dystrophy (FSHD). Previously, this group has shown that the FAT1 gene is misregulated in fetal FSHD1 cases, and identified modifications of the FAT1 gene in FSHD patients without the classical D4Z4 abnormality. Mice lacking a properly functioning Fat1 gene develop muscle wasting specifically in muscles that correspond to the FSHD map.

With the help of funding from the FSH Society, the group has been able to identify specific tissues where Fat1 functions in mice are important for proper muscle development. By removing Fat1 activity in one tissue at a time in mice, they have thus far identified roles for this gene in muscle and non-muscle tissues.

We are now working to understand how muscle degeneration develops and whether Fat1 is required for regeneration in adult animals. This is an essential question for developing potential therapies for patients diagnosed with FSHD.

Current work aims at determining the effect of FAT1 mutations found in FSHD patients and whether they contribute to FSHD symptoms. Ultimately, these DNA alterations could be used as an indicator of susceptibility to disease in individuals without the classical D4Z4 contraction marker.

► LINKING EPIGENETIC ALTERATION AND DUX4 EXPRESSION IN FSHD

Perspective by Kyoko Yokomori, DVM, PhD

Grant title: **Development of a Novel ChIP-Based Diagnostic Assay for FSHD**

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

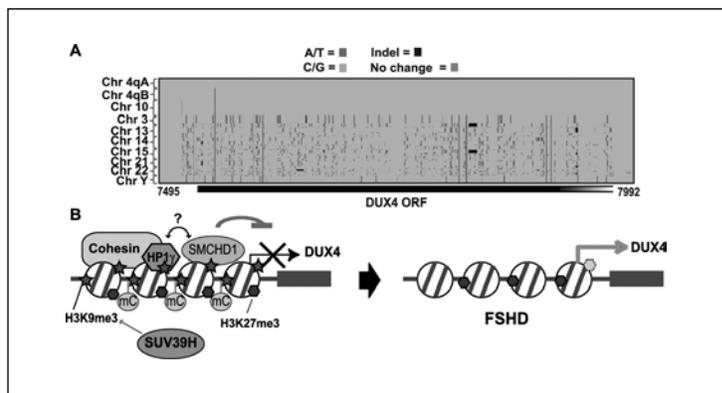
From February 2013: **\$40,000 for one year**

The majority of FSHD cases are associated with shortening of the D4Z4 repeat sequences on chromosome 4q (FSHD1), while less than 5 percent of cases exhibit no repeat contraction (FSHD2).

Recent studies argue that the increased expression of the DUX4 gene embedded in the D4Z4 repeats is critically linked to the development of FSHD. However, how the expression of this gene is altered was unknown. Mutations in the SMCHD1 gene are linked to FSHD2 and severe cases of FSHD1. The SMCHD1 protein normally binds to D4Z4 and represses DUX4 expression. Thus, its mutation contributes to DUX4 dysregulation, though how SMCHD1 is recruited to D4Z4 was unclear.

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 chemically modified (so-called “epigenetic modification”), which affects how genetic information is expressed from DNA. We previously demonstrated that FSHD is an “epigenetic abnormality” disorder signified by the loss of normal histone modification (histone H3 lysine 9 tri-methylation [H3K9me3]) at D4Z4 repeat regions.

In the current paper, we demonstrate 1) the loss of H3K9me3 at D4Z4 results in the loss of SMCHD1 binding and increased DUX4 expression, contributing significantly to FSHD pathogenesis, and 2) although there are D4Z4-like repeats on many other chromosomes, they do not encode the functional DUX4 protein, and H3K9me3 found in those repeats remains unchanged in FSHD, highlighting the distinct role of the D4Z4 chromatin and the DUX4 gene on chromosome 4q in FSHD. [FSHWatch](#)



From “Linking epigenetic alteration and DUX4 expression in FSHD” (Zeng et al. *Hum. Mutat.* (14)). (A) Recent studies argue that the expression change of the DUX4 gene embedded in the D4Z4 repeats is critically linked to the development of FSHD. In the human genome, there are many D4Z4-like repeats that are not linked to FSHD. We found that there are numerous nucleotide changes disrupting the DUX4 gene in these repeats, suggesting that there is selection pressure to preserve DUX4 integrity in the FSHD-linked D4Z4 repeats. (B) We previously found that the D4Z4 repeat cluster normally contains a “heterochromatin” structure specific for repressing gene expression, and that this structure is lost in FSHD patient cells (both FSHD1 and FSHD2). This event is a so-called “epigenetic” change, which is distinct from permanent DNA sequence alteration, and can be reversible. We now demonstrate that artificially disrupting D4Z4 heterochromatin indeed increases DUX4 expression, supporting our model that the loss of heterochromatin in FSHD contributes to inappropriate DUX4 expression. We found that the binding of SMCHD1, which plays a role in DUX4 repression and is frequently mutated in FSHD2, is also sensitive to disruption of heterochromatin. Because epigenetic changes are reprogrammable, our results open up the possibility of controlling DUX4 expression by re-establishing D4Z4 heterochromatin structure.



PAVING THE WAY FOR CLINICAL TRIALS

Unglamorous but essential

by JUNE KINOSHITA
FSH Society

The FSH Society is a vitally important partner with biotech and pharmaceutical companies. Through our website, newsletter, conferences, and smaller events and meetings, the Society brings together patients, families, healthcare providers, and researchers to nurture an engaged, educated community that is required for clinical studies and trials. Every patient and unaffected family member who volunteers for a research study adds to the knowledge that will lead to treatments.

In addition to early-stage drug development research, the FSH Society is investing in biomarkers and clinical trial outcomes criteria, which may not seem as “glamorous” as drug development, but are absolutely critical. These studies are generating the yardsticks by which biotech and pharmaceutical companies will be able to measure whether a drug is effective. These yardsticks need to measure those things that actually make a difference in patients’ lives, and they need to be accurate and replicable from patient to patient, clinic to clinic. Without them, there can be no clinical trials.

▶ EDUCATING AND ENGAGING PATIENTS AT KKI

Perspective by Genila Bibat, MD

Grant title: FSH Society Mid-Atlantic Patient Outreach, Education and Support Group

Investigator: Genila Bibat, MD, Kennedy Krieger Institute, Baltimore, Maryland

From February 2013: \$20,000 over two years

The FSH Society awarded a two-year grant to the Kennedy Krieger Institute (KKI) to establish a well-structured support group for FSHD patients and their families in the Mid-Atlantic area. The quarterly meetings have become a forum for the FSHD community to hear experts talk on topics of interest and a venue for them to socialize.

Since the grant was awarded on February 1, 2013, six meetings were held at KKI which were also made accessible to others via live video streaming. During the inaugural meeting, Dr. Kofi Boahene, Johns Hopkins facial and reconstructive surgeon, spoke about options for FSHD patients to reconstruct facial structures to restore functionality.

Following this, a variety of topics ranging from genetic implications of FSHD and transitioning to adulthood to adaptive sports and recreational activities were discussed. One meeting saw two authorities, Leigh Ann Curl, orthopedic surgeon specializing in scapular fixation, and Shree Pandya, experienced physiotherapist who authored the FSH Society’s brochure for patients and therapists, share their expertise on the needs of FSHD patients.

The current state of FSHD research at KKI and Johns Hopkins

was presented and generated scientific curiosity amongst patients and their families. The meetings, which were well received by the attendees and those who joined via video streaming, resulted in productive interaction between experts and the FSHD patient community.



Kennedy Krieger Institute

▶ ADVANCES IN FUTURE FSHD CLINICAL TRIAL OUTCOME MEASURES

Perspective by Jeffrey Statland, MD

Grant title: Evaluation of an FSHD-Specific Patient-Reported Outcome Measure and a Disease-Specific Functional Rating Scale

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

From August 2012: \$59,185 over two years

Grant title: Pilot Study of Electrical Impedance Myography in Facioscapulothoracic Muscular Dystrophy

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

From February 2013: \$48,909 for one year

Recent breakthroughs in the molecular pathophysiology of FSHD have led to the identification of potential therapeutic targets. Consequently, it has become imperative that appropriate clinical trial tools be in place for FSHD.

We are conducting a single-center pilot and feasibility study to determine the reliability and responsiveness to the change of three novel FSHD-specific outcomes. The first is an FSHD-specific patient-reported outcome measure (FSHDHI). The FSHDHI was developed using survey and interview data from 328 FSHD patients and over 48,000 individual responses. Advanced qualitative methods were utilized to ensure that this instrument address the issues and symptoms of greatest importance to the FSHD community.

The second is a FSHD-specific functional rating scale. We created a 72-point, evaluator-administrated functional scale that reflects the most prevalent and important physical limitations of FSHD.

The final outcome is a novel, non-invasive method of measuring changes in muscle, utilizing electrical impedance myography, a technique commonly used in body composition measurements. We will evaluate 40 participants at four visits over one year. We are currently still recruiting. If you are interested in participating, please contact our study coordinator, Colleen Donlin-Smith, at 585-275-7680.

► **INFLAMMATION AS A POSSIBLE MARKER OF DISEASE PROGRESSION**

Perspective by **Giorgio Tasca, MD**

Grant title: Microdialysis for the Study of Inflammatory Features in Facioscapulohumeral Muscular Dystrophy

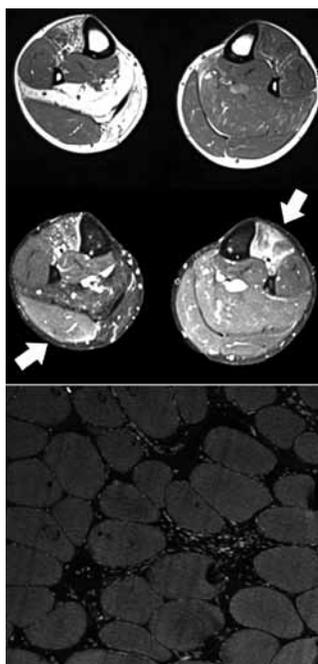
Investigator: Giorgio Tasca, MD, Institute of Neurology Catholic University School of Medicine, Rome, Italy

From August 2013: \$70,000 over one year

There is emerging evidence that inflammation may play a role in the development of muscle damage in FSHD, and this is the field we have been working on in recent years.

The project we are carrying out is aimed at further clarifying the mechanisms and role of inflammation in the early stages of FSHD. We thought to apply a technique, muscle microdialysis, which allows the live monitoring of inflammatory mediators in selected skeletal muscles in a minimally invasive way, and we have already started the procedure on patients and unaffected volunteers. The muscles are selected based on specific features on magnetic resonance imaging (MRI), which is a very sensitive method to detect inflammatory changes and follow phases of activity in FSHD.

We believe and hope that unraveling the significance and contribution to disease progression of inflammation in FSHD could open the way to early and targeted therapies in the near future.



Muscle MRI of the calves in FSHD (top), showing sites of early muscle edema (arrows). These sites correspond to active inflammation on muscle pathology (bottom).

► **USING MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY TO TRACK DISEASE PROGRESSION**

Perspective by **Doris Leung, MD, and Kathryn R. Wagner, MD, PhD**

Grant title: 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

The research team at the Center for Genetic Muscle Disorders at the Kennedy Krieger Institute is very excited about the progress we are making in our research programs. We have completed the first round of enrollment for an observational study of magnetic resonance spectroscopy in individuals with FSHD compared to controls. We are analyzing the data that we have collected (from more than 30 individuals with FSHD and 15 healthy volunteers), and we plan to publish these data soon.

In the past year, we have also launched a new study using whole-body MRI techniques to study the distribution of disease over large regions of the body. We have submitted the preliminary results from this study for publication, and we are seeking to recruit more individuals with FSHD for this study.

Our center is also continuing to recruit: 1) families in which multiple members have FSHD but with differing levels of severity, and 2) asymptomatic individuals who have tested positive for the mutation that causes FSHD. Individuals in these groups have contributed to our research by donating blood and/or muscle tissue, as well as having MRI studies performed. The characterization of this unique group of FSHD patients will provide crucial information on factors that control the severity of disease in FSHD.

Patients and families who are interested in enrolling in these studies should contact Genila Bibat, MD, at 443-923-2778 or bibat@kennedykrieger.org. [FSHWatch](#)



Representative whole-body MRI images showing multiple muscle groups throughout the body. T1-weighted images (leftmost columns) highlight the contrast between fat and muscle, while short tau inversion recovery (STIR) images (rightmost columns) indicate the presence of inflammation in the muscle.



TOWARD TREATMENT DISCOVERY

Tools and techniques for silencing DUX4

by **JUNE KINOSHITA**
FSH Society

▶ ANNUAL
RESEARCH
REPORT

With the identification of DUX4 as a leading target for FSHD drug development, the FSH Society is supporting research projects that employ various strategies to block expression of the gene. In addition, the Society is interested in supporting research to develop additional experimental models—cell and tissue cultures and animals—needed to screen compounds and test how well the strategies are working.

▶ Fisetin suppresses DUX4 expression in FSHD myoblasts

Perspective by **Yi-Wen Chen, DVM, PhD**

Grant title: *Investigating Effects of PARP1 Inhibitors in DUX4 Expression*

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

From August 2013: *\$89,267 over two years*

To date, the aberrant expression of DUX4 protein in muscle cells of individuals with FSHD is believed to be the cause of FSHD. To find out what proteins and mechanisms are involved in regulating the DUX4 expression in the affected cells, we performed a study and identified a protein called poly (ADP-ribose) polymerase 1 (PARP1), which might modulate the expression of DUX4.

We tested several compounds which are known to inhibit PARP1 activities and determined whether the treatments affected the expression of DUX4 in FSHD muscle cells (myoblasts). One of the compounds is fisetin, which is a flavonoid found in various fruits and vegetables such as strawberries, apples, persimmons, grapes, onions, and cucumbers. We are particularly interested in fisetin because this dietary compound has been extensively studied for its antioxidative and anti-inflammatory properties.

Our studies showed that treating cells with fisetin suppressed the expression of DUX4 in the FSHD muscle cells. We are currently testing the compound in DUX4 mouse models. The findings will help us determine whether fisetin may be beneficial to individuals with FSHD.

▶ Gene surgery using TALEN technology

Grant proposal summary provided by **Julie Dumonceaux, PhD**

Grant title: *Gene Surgery Using TALEN Technology: A Therapy for FSHD*

Investigator: *Julie Dumonceaux, PhD, Institut de Myologie, l'Université Pierre et Marie Curie, University of Paris, U974—Inserm, Paris, France*

From August 2013: *\$117,500 over one year*

Two genetic loci for FSHD have been characterized. The first one is located in the subtelomeric region of chromosome 4 and is mutated in 95 percent of FSHD patients (named FSHD1). This region is composed by a 3.3 kb tandemly repeated sequence named

D4Z4. In the general population, the number of repeats varies from 11 to 150, whereas FSHD1 patients carry between one and 10 repeats. The second one is located in chromosome 18, and mutations in the SMCHD1 gene have been found in the majority of the FSHD patients who have normal numbers of D4Z4 repeats (called FSHD2).

Despite the different genetic origins of the disease, all patients are phenotypically indistinguishable and share common molecular features, among them the expression of a protein named DUX4. DUX4 is a transcription factor encoding a potential homeobox protein which is highly toxic after overexpression. DUX4 is present in each D4Z4 unit, but only the unit closest to the telomere (tip of the chromosome) might be able to produce a DUX4 mRNA, stabilized by the addition of the polyA tail induced by 4qA sequences downstream of the D4Z4 array.

Because DUX4 is the common pathogenic target between FSHD1 and FSHD2 patients, our goal is to perform gene editing using transcription activator-like effector nuclease (TALEN) and CRISPR/Cas9 technology to modify the FSHD locus and permanently inhibit DUX4 expression. We have chosen to develop two strategies: 1) to remove the entire D4Z4 array because individuals with such deletions exist and do not present muscular pathology and 2) to mutate the DUX4 polyA signal since it has been shown that a single point mutation in this polyA sequence is sufficient to inhibit DUX4 mRNA expression by modifying its stability.

Specific aims will include: 1) designing nucleases with the best activity and sequence specificity and optimizing the genome engineering strategy; 2) selecting FSHD cells carrying D4Z4 and 4qA sequence modifications for DUX4 inhibition; and 3) testing the therapeutic benefit of D4Z4 genome engineering in appropriate cell culture and animal models by performing several phenotypic measures to assess the consequences of the targeted mutations of the D4Z4 array on FSHD hallmarks.

There are a number of advantages to our proposed approach over other therapeutic strategies currently under investigation for FSHD. There will be no need for repeated long-term administration of treatment since genome editing offers the possibility of permanent correction following transient nuclease activity for the lifetime of the modified cell and its progeny. The benefit of this as a clinical therapy in terms of cost, and toxicological and immunological risk is obvious. Moreover, this approach would be useful for all FSHD cases, whatever the precise mutation/contraction involved.

▶ Our FSHD human induced pluripotent stem cell lines are now available

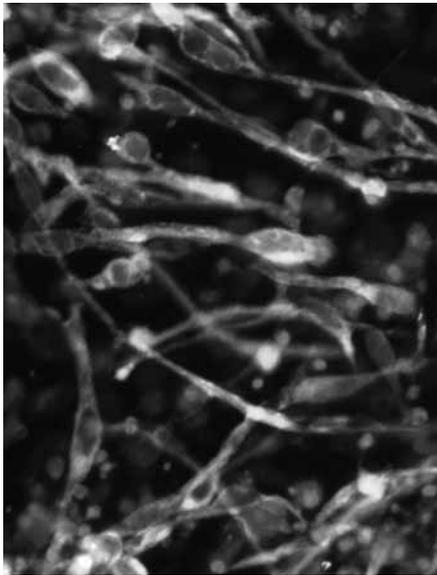
Perspective by **Gabsang Lee, PhD**

Grant title: Derivation of Human Induced Pluripotent Stem Cells From FSH Patient Fibroblasts

Investigator: Gabsang Lee, PhD, Johns Hopkins University, Baltimore, Maryland

From August 2012: \$49,705 over one year

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 (e.g., fibroblasts) of each individual. The first generation of hiPSC technology required infecting the cells with an oncogenic (cancer-causing) virus, but now we don't need to use these viruses. Therefore, it has become feasible to have safe, disease-specific, and autologous hiPSCs



Myogenic cells (myosin heavy chain+ (MF20) (green) derived from FSHD-specific human induced pluripotent cells.

with literally unlimited expansion ability. Thanks to generous support from the FSH Society, my lab was able to generate multiple hiPSC lines from FSHD patients.

However, a key challenge will be to harness the potential of hiPSCs and direct their differentiation into specialized cell types relevant to disease. Recently, we developed a novel methodology to direct hiPSCs into skeletal muscle lineage in a highly defined manner (without using genetic manipulations). Using this approach, we successfully directed FSHD-specific hiPSCs into myogenic cells (see image) with high efficacy. Currently, the FSHD-hiPSC lines are available to the scientific community for research purposes. Please contact the Johns Hopkins Stem Cell Core for further information at SCCF@jhmi.edu.

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

Perspective by Michael Kyba, PhD

Grant title: Exploiting Genome Editing Technology to Modify and Regulate the FSHD Disease Locus

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

From August 2013: \$125,000 over one year

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, they were extremely inefficient, occurring only in 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

... continued on page 18



TOWARD TREATMENT DISCOVERY

... from page 17

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.

▶ ANNUAL RESEARCH REPORT

Since initiating this research project, we have developed tools that allow targeting of a nuclease to the permissive surrounding sequence. We are currently testing these tools to determine whether they actually result in DNA breaks at this sequence and whether they enable the desired template-directed changes.

▶ A TRANSGENIC MOUSE MODEL OF FSHD

Grant proposal summary provided by Peter Jones, PhD

Grant title: **A Transgenic Model of DUX4-Mediated FSHD**

Investigator: **Peter Jones, PhD, University of Massachusetts Medical School, Worcester**

From February 2012: **\$105,000 over two years; \$60,000 year 1, \$45,000 year 2**

The most critical need in the FSHD field is a reliable and faithful mouse model of FSHD. This has been inhibited in the past by lack of a consistent and consensus understanding of the gene misregulation in the human condition that leads to FSHD pathology.

Now that there is widespread agreement about the involve-

ment of DUX4-fl in FSHD pathology, there are different barriers: the severe cytotoxicity of DUX4 and its lack of conservation in mammals. As such, the field has so far failed to generate a genetic mouse model based on DUX4 expression that recapitulates the DUX4-fl expression profile and FSHD-like pathophysiology.

This project proposes to generate a regulable and tunable strain of D4Z4/DUX4 transgenic mice using the Cre/lox system and targeted transgenesis into the Rosa26 locus. Importantly, this model incorporates the downstream cis regulatory elements and DUX4 splicing and polyadenylation of the FSHD-associated 4q35 locus. This is different from any of the mouse models discussed at meetings (none are published) that fail to show any phenotype.

The targeting construct has already been generated and shown to function properly in human and mouse myogenic cell culture and myotubes. With this construct, we believe we can manipulate DUX4 expression in mice 1) to a range of cells in a population (1:50 down to 1:5,000) in the developmental profile of DUX4 expression and/or 2) in any select tissue or spacio-temporal pattern desired.

These mice will prove invaluable for therapeutic screening and understanding DUX4 function. As such, once they are generated and initially characterized we will make these mice available to the FSH community at large in a timely manner for those with therapeutic approaches. **FSHWatch**

Information at your fingertips

The FSH Society's publications for patients are written and reviewed by teams of experts. We are dedicated to making sure you have accurate, useful information to help improve the quality of your healthcare and daily life. You can download these from our website (<http://www.fshsociety.org>) or request printed copies by contacting us at:

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FSHD Patient Brochure (in English)
http://www.fshsociety.org/assets/pdf/PatientBrochure_May2009.pdf

FSHD Patient Brochure (in Spanish)
<http://www.fshsociety.org/assets/html/PatientBrochureSpanish.html>

Exercise, Physical Therapy and FSHD
<http://www.fshsociety.org/pages/patHExer.html>

FSHD: A Guide for Schools
http://www.fshsociety.org/assets/pdf/FSHSociety_FSHDPubs_AGuideForSchools.pdf





The strength I found through physical activity

Sport and physical activity can provide important benefits for our health

by **KRISTIN DUQUETTE**
East Hartford, Connecticut

Earlier this year the American College of Sports Medicine (ACSM) held their first “Developing the Healthy Youth Athlete Conference,” in Buena Vista, Florida. Attendees and speakers—from Nike, Project Play, and Women’s Sports Foundation to NCAA—engaged in dialogue about redefining the healthy youth athlete, best practices for children in sports, and the benefits of physical activity.



Kristin Duquette. Photo taken in July 2012 at Westminster Pool, Simsbury, Connecticut, while filming for *Endless Abilities* documentary.

But is physical activity and training possible for someone diagnosed with a progressive condition? Ten-time Olympic medalist Gary Hall Jr. and I were approached by the conference organizers to discuss this issue and the benefits of sport. Both of us are swimmers from a young age who were diagnosed with a progressive condition. Hall was diagnosed with type 1 diabetes (T1D) in 1999 during the peak of his swimming career, while I was diagnosed with FSHD at age nine. Not only is there no cure for either condition, but at the time there was minimal information or medical studies available to reference for training and physical activity.

Much of our training came with lots of trial and error. With type 1 diabetes, Hall had to undergo glucose monitoring and insulin treatments during his workout sets and competitions. During this process, Hall learned how to maintain a steady insulin level by matching carbohydrates consumed with the amount and level of physical activity.

Training with muscular dystrophy brought its own challenges. With a body having the potential to constantly change, much of my training was finding what strokes should be modified for the best water dynamics in addition to avoiding fatigue.

Another challenge included how to isolate and engage a muscle without compensating from other parts of my body. And with an unconventional body, training and physical activity require innovative thinking from the athlete, parents, coaches, trainers, and doctors.

Having a progressive condition is not only manageable, but one can benefit from physical activity. I had this epiphany a few months after I did not make the 2012 U.S. London Paralympic Team.

Different doctors told me that my training had helped me to maintain my strength and mobility. Swimming was, and will always be, one of the best things I can do for my condition.

Even before I was diagnosed at age nine, swimming as a child established the neural pathways and mental memory in my brain, which became evident when I retaught a different body how to swim after a six-year break. Moving

to national and international competitions not only solidified my commitment to physical activity, but also helped me realize the potential that lies within all of us. No matter the playing field—Olympics, Paralympics, competitions, recreation, or play—physical activity provides a unique opportunity to improve our physical, mental, and emotional well-being.

After my diagnosis, I truly believed I could not be active again. At age 13, I would watch from my couch as professional athletes competed, wishing that I had the ability to swim and race. It took innovation, a support system, and a certain level of stubbornness to ignore society’s limitations and live an active life. I believe this strength to break barriers exists within all of us, a strength that I found through physical activity. FSH Watch

Editors note: Kristin Duquette recently graduated with a BA in Human Rights from Trinity College in Connecticut. She is passionate about disability youth, sport, and empowerment. She is a five-time American Paralympic Record Holder, former US Team Captain for the 2010 Greek Open, and three-time Junior National Record Holder in swimming. Kristin is the founder of a disability empowerment college program called A Day in a Wheelchair, promoting disability rights as human rights. Follow Kristin Duquette on Twitter: www.twitter.com/KristinDuquette.

Adapted from: *The Huffington Post*. Original source link: http://www.huffingtonpost.com/kristin-duquette/strength-through-physical-activity_b_4808607.html

Fundraising How-to Webinar



Have you thought about organizing a fundraising event but don't know how to get off the ground? Check out our series of fundraising “master class” webinars, available for free on the Web. We have held two to date, on auctions with Terry of Colella from Friends of FSH Research on March 14, and on benefit concerts with Judy Seslowe and Beth Johnston on April 4. Keep an eye out for our email invitations. The recorded webinars are also posted on the FSH Society’s YouTube channel. Special thanks to Tony Teel for editing the videos.



Novel mechanisms and tools for FSHD

New Directions Meeting highlights

by **CHARIS HIMEDA, PhD**
 Worcester, Massachusetts

The New Directions in Biology and Disease of Skeletal Muscle Conference, organized by Elizabeth McNally, MD, PhD, and Lee Sweeney, PhD, took place from June 29 through July 2. Held in downtown Chicago's Marriott Hotel, the event brought together researchers, clinicians, and their industry partners to discuss new mechanisms and therapies for muscle disorders.

The overall focus of the meeting was translational, with a strong emphasis on current standards of treatment as well as the status of preclinical treatments and clinical trials. It is well understood that the development of safe and effective therapies requires a strong partnership between academia and industry, and this meeting highlighted the fruits of these coordinated efforts.

In the FSHD session, Silvère van der Maarel, PhD, from Leiden University Medical Center, the Netherlands, described recent work from his group and their collaborators identifying SMCHD1, the gene responsible for most cases of FSHD2 and a modifier of disease severity in several cases of FSHD1.

SMCHD1 is a protein that acts as an epigenetic regulator, establishing heritable patterns of gene expression. While the expression patterns mediated by epigenetic factors are stable enough to be inherited through cell division and over the long term, these states can also be dynamic and reversible, making epigenetic factors a prime target for therapies.

In healthy individuals, SMCHD1 represses expression of the DUX4 gene, which is toxic in skeletal muscle. In FSHD2 patients, this function is lost, leading to inappropriate DUX4 expression and consequent pathology. FSHD is marked by highly variable severity and penetrance (proportion of genetically FSHD individuals who exhibit clinical symptoms), and van der Maarel pointed out that different patients are likely to have different epigenetic susceptibility to disease based on mutations in SMCHD1 and other modifier genes.

Peter Jones, PhD, from the University of Massachusetts Medical School expanded upon the role of epigenetics in FSHD, presenting unpublished work characterizing the levels of DNA methylation of the DUX4 gene. DNA methylation, mediated by proteins such as SMCHD1, generally represses gene expression, and Jones demonstrated that levels of methylation at the DUX4 gene correlate with the severity of clinical phenotype in FSHD patients. Healthy individuals displayed much higher levels of methylation than affected FSHD patients, and individuals who are genetically FSHD, but have no symptoms, displayed distinctly intermediate levels of methylation. Since methylation levels are variable among individuals, this work also stressed the importance of using family cohorts in comparative studies.

Scott Harper, PhD, from Ohio State University presented unpublished data showing activity of the DUX4 promoter (proximal region that drives DUX4 expression) in mice injected with a construct expressing a reporter gene driven by this promoter. The DUX4 promoter is active in a number of tissues, including skeletal muscles affected in FSHD, displaying the asymmetry and variability in expression levels seen in FSHD patients. A mouse model that dis-



Chicago, site of the New Directions in Biology and Disease of Skeletal Muscle Conference in June 2014. Photo by Charis Himeda.

plays the physical characteristics of FSHD remains a critical need in the field, and development of Harper's transgenic model, in which DUX4 will be inducibly expressed (expressed under the control of an inducing molecule) from its homologous promoter, is currently underway.

Rabi Tawil, MD, from the University of Rochester presented data from a small exploratory study looking for FSHD biomarkers (measurable molecules that correlate with disease status) in blood and emphasized the need for further validation of promising candidates in a larger study.

Jeff Miller, PhD, from Boston University described unpublished data showing a new role for DUX4 in dysregulation of the ubiquitin-proteasome system for protein degradation, and Lou Kunkel, PhD, of Boston Children's Hospital described his zebrafish model of FSHD, with an emphasis on using the model for high-throughput drug screening.

The meeting included many updates on clinical trials for muscular dystrophies, both from representatives of pharmaceutical companies and from academic researchers. While most presentations focused on Duchenne muscular dystrophy (DMD), Charles Thornton, MD, from the University of Rochester described progress on clinical trials for myotonic dystrophy (DM). Earlier work from a team led by Thurman Wheeler, MD, demonstrated that knock-down of a toxic mutant mRNA by antisense oligonucleotides led to prolonged correction of

It is becoming increasingly clear that there are many paths to a complex disorder, as the list of causative genes for the limb girdle muscular dystrophies and the nemaline myopathies continues to grow.

whole-body myotonia in a mouse model of DM. In a collaboration between Isis Pharmaceuticals and Genzyme, thousands of antisense oligonucleotides were screened to identify optimal candidates, and Phase 1 trials opened in June of this year.

Antisense strategies for correction of DMD and spinal muscular atrophy were also discussed, several in the early stages of clinical trials and each a collaboration between academic researchers and their partners in industry. These efforts are relevant to potential treatments for FSHD, as one valid avenue for therapy is knock-down of DUX4 or its gene targets in skeletal muscle.

It is becoming increasingly clear that there are many paths to a complex disorder, as the list of causative genes for the limb girdle muscular dystrophies and the nemaline myopathies continues to grow. Additionally, different mutations in the same gene can give rise to very different disorders, as in the case of the laminopathies, which encompass diseases of striated muscle, fat, the peripheral nervous system, and multiple body systems.

These sessions also underscored an ever expanding appreciation for the role that modifier genes, both genetic and epigenetic, play in disease progression and clinical phenotype. While genetic targets for therapy are likely to be disease specific, targeting epigenetic regulators might be more effective for the treatment of multiple diseases.

One thing is certain: Progress in any muscle disorder is progress for all, since many therapeutic avenues and technologies are broadly applicable, as are lessons learned at all stages of therapy development. **FSHWatch**

Editor's note: Charis Himeda, PhD, holds the title of Research Associate II at the Wellstone Program, Department of Cell and Developmental Biology, University of Massachusetts Medical School in Worcester.

A natural thing—A simple chain
Minute information tells my future—sort of...
What will it mean to me? What will it matter?
It proved true today—so now where will the chain lead me?

A natural thing—this chromosome chain
Now I know mine misses a thing or two... or more
And sets in motion my non-stop event
What will it mean to me? What changes are ahead?

I have already lost what you have....
Already cannot hear what you said... but I smile
Do you know—or not? Can you tell? Not sure?
What will that mean to me? What will it matter?

This missing piece does not hide so well...
Soon you will see that too... and I will still smile?
Do you feel sorry for me? Do I want you to?
Do I feel sorry for me? I don't know....

This chain is strong—I must comply
A simple thing... a natural thing
I am not the same as you
I am not the same as me anymore

A natural thing... to miss some things
Makes me less than what you are
I know the high road and what I should seek
But deep inside I see—I am less of what you are

I hurt more—because there is less of me
Inside this natural thing—this genetic chain
Repeats are small—I know what it means
You do not know do not feel do not hurt

And so I am slow—I drop some things
I get tired—I smile—I do not hear
But I see inside—Do you?
Life goes on—A natural thing

This FSHD.... that genetic chain...
And now, it is mine—a natural chain.

— MISSY CASSIDY,
EDGEWATER, MARYLAND

Author's note: For several years I suspected I might have FSHD, as my brother had it confirmed through genetic testing. Like him, my symptoms were not apparent until later in life. I had spent my youth and adulthood very active—rock climbing, white water canoeing, and raising a family. But I guess I knew based on what I was experiencing in the last few years—pain, weakness, losing range of motion, tripping—that this genetic test would come back positive. Knowing what I do by virtue of my brother being so informed and active in clinical trials, I was not surprised. But you know, it just kind of takes your breath away to read those words in a clinical report. And so I found myself late at night reading it again and again. This poem is really just an expression of feelings I had that night. I wrote it out more as a way of coping, not looking for pity. The questions all led to more questions. They still do. But I am positive about my search. And not every day is perfect. I hope sharing these feelings, and I am no poet, might help others see there are a lot of us out there.

FSHD research in the spotlight

2014 American Society for Gene and Cell Therapy Conference

by **AMANDA RICKARD**
Seattle, Washington

We live in an era of breathtaking biological discovery, where genetic manipulation is no longer relegated to the realms of imagination and science fiction. At the 2014 American Society for Gene and Cell Therapy (ASGCT) Conference in Washington, DC, held May 21 to 24, there were presentations on assorted tools to move, edit, and delete genes in live cells. Some researchers are also developing therapeutic strategies that will allow cells to be taken from a person with a disease, transformed into healthy cells in the lab, and then returned to the donor, thereby treating the disease.



Amanda Rickard

Seeing this kind of innovation is incredibly reaffirming and inspirational, and data from experiments such as these can inform biologists who study any number of diseases on how to proceed with similar research.

Attending conferences also affords a chance to engage in a sometimes frightening, but pivotal part of science: presentation of my own work, as part of the research process that scientists call peer review. At ASGCT I was able to present on a system that both allows me to watch the effects of DUX4, the gene that causes FSHD, in live FSHD cells under a microscope, and gives the potential to test hundreds of prospective treatments at once.

Presentations are an important chance to hear direct feedback and constructive criticism from a diverse and objective audience, to learn how to explain my projects clearly, and to participate in open discussions about my data. At conferences I also get the chance to contribute to others' work by helping fellow scientists think critically about their own projects.

Because research is often frustrating and arduous, scientists also use conferences as an opportunity to recognize leaders who have worked very hard and made great progress in their field. At ASGCT, FSHD researcher Scott Harper of Ohio State University was recognized with an Outstanding New Investigator

award (see story on page 6).

Harper gave an acceptance speech that detailed his work on FSHD—a great moment for all of us because of the resulting exposure for our underfunded and understudied disease. About 1,700 scientists from all over the world, from senior pioneers in the field of gene therapy to young up-and-comers still deciding on projects to pursue in their future careers, may now consider tackling some of the outstanding questions in FSHD research.

Even if they don't study FSHD, the people who attend ASGCT have the same goals as those of us who do: to create models of a disease, to find treatments that cure the models, and to move those treatments into safe clinical trials for patients. Because of our common approach, we can learn from each other's successes and challenges.

Researchers presented amazing work that is directly relevant to FSHD, including

in patients with FSHD.

Seeing so much progress toward cures or treatment of many diseases is really motivating. Groups showed data on effective treatments in humans for diseases including Parkinson's and hemophilia, and in models of spinal muscular atrophy, Duchenne muscular dystrophy, myotubular myopathy, and many others.

We saw our field's first goals met with a presentation by Joel Chamberlain of the University of Washington about delivery of DUX4 to a mouse's muscle and the observation of FSHD-like changes there, and with Scott Harper's mouse model system in which he replaced the toxic part of DUX4 with a protein that glows green, lighting the areas damaged in FSHD. Our next step is to find treatments to test in these models, which is on the horizon thanks to work in many labs, including ours.

“Seeing so much progress toward cures or treatment of many diseases is really motivating. Groups showed data on effective treatments in humans for diseases including Parkinson's and hemophilia, and in models of spinal muscular atrophy, Duchenne muscular dystrophy, myotubular myopathy, and many others.”

AMANDA RICKARD



the best ways to develop animal models of muscle diseases, new designs for therapeutic viruses to ensure that they are safe and work well in muscle, stem cell therapies for muscle healing, and insights into when and where we should deliver these treatments to be most effective.

Researchers studying many diseases were excited about the use of the Cas9/CRISPR system for editing and controlling diseased genes more easily. These new tools can directly edit DNA or function as “volume knobs” for controlling genes whose metaphorical dials are turned the wrong way, as DUX4's volume is turned too far

Overall, gene and cell therapies are seeing exponential increases in interest and success, much like FSHD research. I hope to have a chance to attend more conferences like this one, where cutting-edge technology shows incredible promise in effectively treating patients. Next year's ASGCT meeting will be held in New Orleans (May 13 through 16, 2015), and there's no doubt that it will be filled with more stories of success (and, with any luck, a couple of crawfish boils). [FSHWatch](#)

Editor's note: Amanda Rickard is a research scientist in the laboratory of Daniel Miller at the University of Washington in Seattle.

NEW CENTER TO DESIGN THERAPIES FOR MUSCULAR DYSTROPHY DISORDERS

... from page 1

Previous studies led by Chamberlain have shown that gene therapy can eliminate Duchenne muscular dystrophy in rodent models of the disorder. He and his colleagues are working to apply those findings to clinical applications for patients with the disease. Other studies will seek better rodent models for FSHD to adapt the gene therapy strategies for a wider range of muscular dystrophies. The new center will also support patient studies on the causes and mechanisms behind the disease's progression.

One of the first of these clinical trials will be an imaging study to explore inflammation and markers of disease progression in FSHD. Tapscott led earlier studies that elucidated the cause of FSHD. The current work aims to advance that knowledge into clinical application. As an initial step, a magnetic resonance imaging, or MRI, study of individuals with the disease will be led by Dennis Shaw and



The Fred Hutchinson Cancer Research Center in Seattle, Washington

Leo Wang at the University of Washington and Seattle Children's, with Rabi Tawil at the University of Rochester, to evaluate and validate biomarkers in the disease.

Duchenne muscular dystrophy and FSHD are both among the most common inherited human disorders. Duchenne muscular dystrophy primarily affects children; FSHD more commonly first appears during

adolescence or adulthood. While a defective gene critical for muscle strength causes Duchenne muscular dystrophy, a toxic protein produced in muscle causes FSHD.

The new effort is one of the nation's Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers. It is funded through a four-year, \$6.3 million grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, a branch of the National Institutes of Health.

The National Institutes of Health, Friends of FSH Research, the Muscular Dystrophy Association, Edgar Martinez, and the Pistol Creek Research Foundation supported the preliminary studies leading to the formation of the new center. [FSH Watch](#)

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FSHD IS ONE OF THE MOST PREVALENT NEUROMUSCULAR DISORDERS

... from page 1

the Netherlands for many years has had a robust and well-documented registry with widespread participation, and so there is a good likelihood the study is accurate, at least for the Dutch population.

The new Dutch study employed a method called "capture-recapture," commonly used to estimate the size of wildlife populations. With this method, one might capture and tag a large number of turtles, let's say, and then release them back into their pond. One would then capture a second group of turtles from the same pond. A fraction of these newly caught turtles would carry tags, showing that they were part of the first group. From these data, a statistician can calculate the total population of turtles in the pond.

The Dutch team used three large, national registries of neuromuscular disease and genetics to "capture" FSHD patients and then, using patients' initials and birthdates as the "tags," were able to determine the degree of overlap among the three registries.

This capture-recapture analysis allowed them to calculate the incidence of FSHD—that is, the number of newly diagnosed cases per year. They found that the mean

age at diagnosis among the registered FSHD patients was 42 years, and with an average life expectancy of 39 years from the age of diagnosis, they concluded that the prevalence (number of individuals with FSHD) was 12 in 100,000.

"This study shows that the total number of symptomatic persons with FSHD in the population may well be underestimated, and a considerable number of affected individuals remain undiagnosed," the study's authors conclude. "This suggests that FSHD is one of the most prevalent neuromuscular disorders."

Importantly, the study indicates that a large proportion of individuals with FSHD are not being diagnosed—and therefore are not getting counted. One reason is that many have mild symptoms that go unnoticed by themselves and their doctors. Another is that FSHD patients are told there is nothing that can be done for them. Knowing this, their relatives who exhibit symptoms may not bother to seek a doctor's diagnosis or care.

Does any of this sound familiar from your own experience with family members? These are serious challenges for the FSHD community. If the numbers of affected

individuals are undercounted, this makes it more difficult to raise the resources and investment needed to combat the disease.

The tens of thousands of mildly affected individuals who are not being counted, and not volunteering for research, are also the same individuals who may hold the keys to aid the more severely affected. They may have genetic or other factors that have protected them—factors that could provide insight for future treatments.

The fates of people with FSHD across the spectrum, from the mildly to the most severely affected, are inextricably bound together. How can we foster a sense of urgency around joining forces to solve this disease? It's time to start having these conversations. Please consider speaking with your undiagnosed family members and encouraging them to reach out to the FSH Society so they can be counted. Thank you! [FSH Watch](#)

References

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2014 fall events

Raising funds and awareness

September 29: Festive Evening of Song, a benefit auction and concert with Steven Blier and two-time Grammy award winner Sylvia McNair. Tappan Hill, Tarrytown, New York

October 3: Third Annual Hustle4Muscle Golf Tournament. Abilene, Texas

October 5: Cosie Laurello Memorial 10K Run. Geneva, Ohio

October 11: Fireside Chat, pre-Celebrity Walk 'n' Roll event. Irvine, California

October 12: Fifth Annual Celebrity Walk 'n' Roll. Irvine, California

October 17-18: FSH Society International Research Consortium Conference. San Diego, California

October 18: FSHD Champions Annual Meeting. San Diego, California

November 15: Friends Supporting Hope Benefit Dinner. Boston, Massachusetts



Two-time Grammy Award winner Sylvia McNair performed at the Festive Evening of Song this September 29 with pianist Steven Blier. McNair lays claim to a three-decade, stellar career in the musical realms of opera, oratorio, cabaret, and musical theater.

GET SOCIAL!

Join our online communities to get news, ask questions, and seek advice and support from fellow FSHD patients and family members. The FSH Society Yahoo! Groups forum has tens of thousands of searchable posts. Bookmark these pages and come back often. To find the FSH Society Facebook page and Yahoo! Groups, go to these sites and search for "FSH Society." If privacy is a concern, you can use your account privacy settings to limit who can see your posts. You can also follow us on Twitter @FSHSociety.

MATCHING GIFTS AND OTHER WORKPLACE GIVING

Many employers offer workers options for directing the company's funds to a charitable organization of their choice. When this opportunity is available to you, please consider how your workplace might make a gift to the FSH Society. This is a great way to double, triple, or even quadruple your gift!

CHARITY NAVIGATOR TOP PERFORMER

The FSH Society has been awarded its sixth consecutive Four-Star rating by one of the nation's leading charity watchdog organizations, Charity Navigator, and was named one of America's 10 Charities Worth Watching. Charity Navigator's Four-Star Award—its highest—indicates that the FSH Society consistently executes its mission in a fiscally responsible way and outperforms most other charities in the United States. www.charitynavigator.org



AMAZON SMILE—PAINLESS GIVING!

If you shop on Amazon, just use the Smile portal (<http://smile.amazon.com/>), follow the prompts to select the FSH Society as your charity of choice, and Amazon will donate 0.5 percent of every purchase you make! If every FSH Society member shopped with Smile, these micro-donations would add up to tens of thousands of dollars a year!



COMBINED FEDERAL CAMPAIGN (CFC), 2014 CAMPAIGN

The CFC is the world's largest and most successful annual workplace charity campaign, with more than 300 CFC campaigns throughout the country and internationally to help raise millions of dollars each year. Pledges made by federal civilian, postal, and military donors during the campaign season (September 1 to December 15) support eligible nonprofit organizations that provide health and human service benefits throughout the world. The FSH Society's identification number is 10239.

HAVE YOU MADE A GIFT TO THE SOCIETY THIS YEAR?

Your generous support makes a real difference! Please return your gift in the enclosed envelope. Or contribute online at <http://www.fshsociety.org>. You can make recurring monthly gifts as well as gifts in tribute of a loved one or friend. Thank you!



OUR EBAY CHARITY AUCTION SITE

The FSH Society is registered (as the "FSH Muscular Dystrophy Society") on eBay's charity auction site. If you have an eBay seller's account, you can put items up for auction and direct from 10 to 100 percent of the proceeds to the Society. <http://givingworks.ebay.com/charity-auctions/charity/fsh-muscular-dystrophy-society/58335/>

