**Connect the community of patients, families, clinicians and investigators**

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**DUX4 and FSHD:**

**How the FSH Society Connects the Research Community**

By Alexandra Belayew, Ph.D., University of Mons-Hainaut, Mons, Belgium, and Alberto Rosa, M.D., Ph.D., Institute for Medical Research “Mercedes y Martín Ferreyra” INIMEC-CONICET, Córdoba, Argentina

In 2007, DUX4 emerged as a candidate gene for FSHD. DUX4 is from a family of regulatory and developmental genes and stands for D4Z4 homeobox gene 4. D4Z4 has been found to reside inside of each repeat of the D4Z4 repeat array. When an individual has ten or fewer D4Z4 repeats he or she can have FSHD.

DUX4 research has an interesting history going back to the mid-late 1990s and the FSH Society has been instrumental in advocating and funding research on DUX4 in five different countries. The scientists working on DUX4 have persevered despite difficulty in obtaining funding and getting papers accepted for publication. The FSH Society facilitated the connections leading to progress in understanding the role of DUX4 in facioscapulohumeral muscular dystrophy by funding research grants and travel grants and enabling researchers to connect to one another through our website and our annual research symposium. The FSH Society’s staff and scientific advisory board also work actively with researchers to help with networking and connections.

The story of Alexandra Belayew, Ph.D., begins in Belgium. Prior to developing an interest in muscular dystrophy research, Dr. Belayew was heading a small group in the laboratory of Prof. Désiré Collen, a renowned scientist and medical doctor at the Catholic University of Leuven in Belgium. Prof. Collen was famous for his discovery of a protein named tPA (tissue plasminogen activator) used to re-establish blood flow in blocked arteries. Hundreds of thousands of individuals have benefited from Prof. Collen’s discovery. At that time, Dr. Belayew was studying a protein named HLTF which has the characteristics of a “transcription factor” (a protein that controls the expression of one or more genes).

Another scientist in Dr. Belayew’s laboratory, Hao Ding, Ph.D., a physician from China, was working on his Ph.D. thesis under Dr. Belayew’s supervision. Dr. Belayew explains, “Dr. Ding has an amazing work ethic. He was always testing out new ideas in the off hours when the lab was nearly empty. One Monday morning, at a research meeting, Dr. Ding explained that he had set up an experiment to go “fishing” for all the genes onto which the HLTF protein was bound in the cell. Such experiments, named chromatin immunoprecipitation (ChIP), are now routinely done in labs, but at the time, there was no kit for it and the amount of work involved was quite impressive.” Dr. Belayew spent an entire night on her home computer searching Internet databases for sequences similar to approximately one hundred DNA fragments that bind the HLTF isolated by Dr. Ding. “It was very frustrating because at the time Internet connections were very slow, and only a small part of the human genome was known.” However, at last she identified a sequence that looked very much like a

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**Patients and Families To Gather In Iowa City/Coralville: July 27, 2008**

The 2008 International Patient Conference will be held at the Marriott Hotel and Conference Center, Coralville, Iowa, on the banks of the Iowa River, one mile from University of Iowa Hospitals and Clinics and minutes from downtown Iowa City.

Iowa City is home to the University of Iowa Hospitals and Clinics and the UI Roy J. and Lucille A. Carver College of Medicine, a comprehensive academic medical center that is distinguished internationally. For 16 years, the UI Hospitals and Clinics have been recognized as one of “America’s Best” by U.S. News and World Report.

Iowa City and Coralville are within easy driving distance of major Midwestern cities and served by airports in Cedar Rapids, the Quad Cities, and Des Moines (see map page 2). These eastern Iowa communities, energized by academic and artistic prowess, and outdoor recreation, are in close proximity to charming farm communities that document our rural heritage. Many vacation, sightseeing, and other leisure opportunities are available.

The conference will begin with registration and a buffet breakfast at 8:00 a.m. on Sunday, July 27, and conclude by 5:30 p.m.
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Informal reception and greeting will be available on Saturday from 4:00 p.m. to 7:00 p.m. at the hotel; a continental breakfast and send-off will be available on Monday, July 28, 8:00 a.m. to 10:00 a.m.

Lectures and panel discussions are planned to bring the most current advances in FSHD research to the FSHD community of patients, families and scientists. There will be formal and informal forums to advance knowledge, understanding and provide support and networking. The reception, continental breakfasts and a luncheon are included in the registration fee: $80 each for adults, $40 each for children ages 12-18, and children under 12 years of age, free. More details will be made available on the Society’s website as planning proceeds.

For hotel reservations, go to www.marriott.com/cidic. The Society’s group code is fshfsha. For telephone inquiries, call (319) 688-4000 (Coralville), or Marriott reservations at 1 (800) 228-9290. The hotel is holding a block of rooms at $99.00 per night (single, double, triple, or quad), plus taxes and parking. This is a new facility and is fully ADA-compliant with accessible and equipped guest rooms. Recreation facilities including the pool are accessible. For the best selection of rooms, please make your reservations early. The closing date for the Society’s block of rooms is June 27.

SAVE THE DATE
A Gathering of FSH Society Members
New York Botanical Garden
April 22, 2008
6:00 p.m. Cocktails · Dinner to follow.
An evening for members of the FSH Society in the tri-state area, and beyond, to meet each other and to hear a brief program about research and clinical advances in FSH Muscular Dystrophy.

Menu and evening generously hosted by Abigail and Robert Kirsch
There will be no solicitation of funds at this event.
Attendance limited to individuals with current membership, 2007 or 2008.

Invitation to follow. For more information, or to reserve a place now, please call (617) 658-7878 or email nancy.vanzant@fshsociety.org.

The FSH Society is a 501(c)(3) organization dedicated to solving facioscapulohumeral muscular dystrophy.
Katherine Mathews, M.D., to Offer Clinic for Infantile FSHD, July 28, 2008

Katherine Mathews, M.D., Pediatric Neurologist, and other staff at the University of Iowa Hospitals and Clinic will offer a clinic for infantile FSHD patients on July 28, 2008. To express interest in the clinic, please email Jenny Lazzaro at jennifer.lazzaro@fshsociety.org.

To read more about Dr. Mathews, please refer to her interview in FSH Watch, Fall 2007.

Society Welcomes David J. Glass, M.D., to the Board of Directors

William R. Lewis, Sr., M.D., Chairman, welcomes on behalf of other members, David J. Glass, M.D., to the Society’s Board of Directors. Dr. Glass is Global Head, Muscle Diseases, Novartis Institutes for Biomedical Research, Cambridge, Massachusetts. Prior to joining Novartis, he was Vice President for Muscle Diseases at Regeneron Pharmaceuticals, where he worked for 14 years. He holds an M.D. from New York Medical College and conducted postdoctoral work at Columbia University. He is the co-author of more than 50 peer-reviewed research articles on cell signaling mechanisms in neuromuscular disease, obesity, and cancer.

We look forward to the service Dr. Glass will bring the Society and the FSHD community.

A Letter from the Chairman, Board of Directors, FSH Society

February 2008

Dear Friends,

In November, I wrote to you to invite you to participate in the Challenge of Hope, my family’s challenge to FSH Society members and to the FSHD community. I am delighted that you have made so many gifts, often new and larger gifts, to match this challenge.

As you may recall, we offered to match your gift and the gifts of others on a dollar-for-dollar basis if you made your gift by December 31. As is reported elsewhere in this issue of Watch, the Challenge has been met, and my wife and I have made our gift of $100,000 to the FSH Society, specifically to support post-doctoral research.

Together over 250 individuals, foundations and businesses in the FSHD community contributed $190,000. As you can see from the Donor Annual Report included in this issue, many people have been generous with gifts large and small. I’d like to especially thank the Kelly Family, Howard Chabner, Marshall Gillespie, Jeffrey Jacobs, Christopher Stenmon, and Bill and Judy Herzberg for the many generous gifts they have solicited from their friends and family on behalf of the FSH Society in 2007.

All our gifts have advanced patient services, education and outreach, advocacy, and research—all critical to the work of the Society and our community.

Researchers continue to be hard at work looking for the gene or genes that cause FSHD, and some investigators are using animal models to try experimental therapies. We are optimistic that this work can lead to a cure for FSHD and treatments for patients.

On behalf of all the patients and their families, thank you for supporting the Society.

Sincerely,

William R. Lewis, Sr., M.D.

The Challenge of Hope Raises $290,000 and Exceeds the Goal!

In late 2007, Dr. and Mrs. William R. Lewis, Sr., offered a challenge gift to the Society and to our members. They agreed to match member gifts on a dollar-for-dollar basis if gifts were made by December 31 – up to a total of $100,000. By mid-December, the Challenge goal was reached, but many people had not yet had a chance to participate. Four members of the Board of Directors agreed to issue a “supplemental” challenge to match gifts yet to come.

This was the Challenge of Hope. Many people renewed their 2007 memberships and helped to meet the Challenge of Hope. Others who had already renewed their memberships, made another gift to the Society for FSH muscular dystrophy. The Lewises were eager to see new members coming into the Society and members increasing their gifts. Together with Dr. and Mrs. Lewis’ gift, the Challenge brought $290,000 in gifts to the Society at year’s end.

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DUX4 and FSHD, continued from front page

Alberto Rosa, M.D., Ph.D.,
Institute for Medical Research
“Mercedes y Martín Ferreyra,”
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gene promoter and was referred to as “similar to the FSHD locus.” Dr. Belayew had never heard of FSHD, nor had anyone else in the lab.

A young Flemish graduate student named Jan Gabriëls had recently joined the team; he was a bioengineering graduate with considerable computer facility. He started a search for “FSHD” using an early version of Netscape (it would be many years before Google made Internet surfing easy for everyone). His search led the lab to the FSH Society website and another online genomics database. It turned out that Dr. Ding’s sequence was similar to a part of the D4Z4 element repeated in tandem at the FSHD locus. This D4Z4 sequence had been provided to the database in 1994 by a team in the U.K. lab of Jane Hewitt, Ph.D. It was considered “junk” because it was repeated DNA segments and such repeated elements are found all over the chromosomes and are not considered to contain any gene. However, Dr. Hewitt had identified a putative gene coding for a protein that nobody had described before. Her team had made numerous attempts at finding any gene expression that would come from D4Z4, without success. Dr. Hewitt had found an open reading frame with a double homeobox that is the “recipe” to make a protein but she was unable to find its promoter that is the beginning of the gene. Dr. Hewitt left this line of inquiry for lack of evidence that a gene might be present in D4Z4. Dr. Ding, however, found that the promoter he had isolated corresponded to a part of Dr Hewitt’s open reading frame, so that D4Z4 may potentially express a shorter protein they called DUX4. This protein has the characteristics of a “transcription factor” (a protein that controls the expression of one or more genes). Also, the protein has two sequences called homeodomains which are present in proteins that participate in muscle formation and regeneration. Dr. Belayew contacted Dr. Hewitt, who immediately invited her and Dr. Ding to visit her lab in Manchester. After a lively discussion, Dr. Hewitt formulated the following hypothesis: “in non-affected individuals, DUX4 is not expressed because the large number of D4Z4 elements is in a tight chromatin structure; in FSHD patients this chromatin is open–because of the small number of D4Z4 copies–leading to DUX4 activation and production of a toxic protein that kills the muscle cells”. Dr. Belayew contacted Daniel Paul Perez, who invited her to an upcoming FSHD research meeting in Denver, Colorado, to present her data to the entire FSHD research community.

Dr. Belayew’s team continues to work on this hypothesis. With assistance from the FSH Society, she has reached clinicians who have provided DNA and cells from patients. Today she is at the University of Mons-Hainaut (Belgium) and together with her co-PI, Frédérique Coppée, Ph.D., and graduate student, Eugénie Ansseau, she has finally demonstrated that FSHD muscle cells produced the DUX4 messenger RNA. Dr. Belayew’s initial FSH Society funding has led to other grants from the Association Française contre les Myopathies, MDAUSA and the National Institutes of Health.

Studies show that DUX4 is a major candidate for the pathogenesis of FSHD. Current work performed at the laboratories of Dr. Rosa and Dr. Belayew and several other laboratories on DUX4, should rapidly increase our knowledge about this mysterious protein and its potential role in FSHD.

Meanwhile, in Argentina and unknown to Dr. Belayew, a research team was working on DUX4 and FSHD under the direction of Alberto Rosa, M.D., Ph.D. Dr. Rosa tells his story: “when I was 16 years old and in my last year of high school, I was interested in both scientific research and clinical medicine. First I obtained an undergraduate degree in biochemistry and a Ph.D. in molecular biology—part of that training in an institution led by the Argentinean Nobel Laureate L. F. Leloir, M.D. In 1988, I started my own research laboratory and, for several years, studied basic genetic phenomena in fungi.” Dr. Rosa then obtained a degree in medicine and his second Ph.D., at the University of Cordoba, the oldest university in Latin America. “After obtaining my M.D, I wished to follow my high school dream: to link the fields of basic science and clinical medicine in Argentina. I was particularly encouraged by the exciting progress in the study of the human genome. My previous research interest in fungi was the epigenetic bases of gene expression. I started working on ICF, a human syndrome connected with DNA methylation, which is a form of epigenetic control in mammals.”

During this period, Dr. Rosa was awarded an international research scholarship by the Howard Hughes Medical Institute and held posts as visiting professor at universities in the U.S. and Europe, including the laboratory of Judith Melki, M.D., Ph.D., in Strasbourg (France). Dr. Melki directed the group that discovered the gene SMN1 (for the disease called spinal muscular atrophy). At the scientific library in Strasbourg, Dr. Rosa found a copy of the recent thesis by Judith van Deutekom, Ph.D. (Holland), concerning the genetic characterization of the locus FSHD at 4q35. Upon reading the thesis, he became fascinated with the scientific
**DUX4 and FSHD, continued from page 4**

challenge offered by a potential epigenetic control underlying the pathogeneses of FSHD. Dr. Rosa realized that his background of change in chromatin structure in fungi would relate directly to FSHD and could be a human disease model of his previous research efforts. Just a few months later, his laboratory in Argentina began to offer molecular testing for FSHD. His laboratory and that of Mayana Zatz, M.Sc., Ph.D., in Brazil, are the only sites performing molecular testing for FSHD in Latin America.

In January 1998, Dr. Rosa’s Ph.D. student, Valeria Kowaljow, began exploring the potential pathogenic role in FSHD of a putative toxic protein encoded by the tandem repeat D4Z4 at 4q35. Based on his previous experience with the gene eth-1 in the fungus N. crassa, Dr. Rosa considered that an inherited dominant trait—as observed in FSHD—should not be explained by a “repressive” mechanism but based on a “toxic gain of function” phenomenon, perhaps explained by abnormal epigenetic control of a gene in a relaxed chromatin environment.

A few months later, a paper (Gabriëls et al., 1999) was published by Dr. Belayew’s group proposing a similar hypothesis: DUX4 may be a toxic over-expressed protein causing FSHD!

Dr. Rosa and Dr. Belayew met for the first time at the International Workshop of the FSH Society in Los Angeles, in 2003. At that meeting, Dr. Rosa presented exciting research news in FSHD: he and Kowaljow had found in Argentina that DUX4 is a toxic protein when expressed in cultured cells. They showed that DUX4 is located in the cell nucleus—a finding also reported by Dr. Belayew’s group—and kills the cells by a phenomenon called apoptosis. Everyone at the meeting was excited by the research results, particularly Belayew and Rosa, who learned that their years of work on identical hypothesis were producing important results. Dr. Rosa and Dr. Belayew decided to join efforts to continue studying the toxic effect of DUX4. The FSH Society and the Association Française contre les Myopathies have supported both groups, including a visit of Dr. Rosa to Dr. Belayew’s laboratory in Belgium. Their joint efforts have led to the confirmation of the apoptotic nature of DUX4 mediated cell death.

They have also demonstrated that DUX4-mediated toxicity is specific for this protein—i.e., other proteins similar to DUX4 do not have a toxic effect. Both groups had great difficulties getting their research findings published independently—but the paper submitted jointly was accepted for publication in the journal *Neuromuscular Disorders*. This also happened in connection with the recent discovery by Yi-Wen Chen, D.V.M., Ph.D. (see Fall 2007 *Watch*), who had a difficult time having her work published but has experienced success jointly publishing with Dr. Belayew. Taken together, their studies show that DUX4 is a major candidate for the pathogeneses of FSHD. Current work performed at the laboratories of Dr. Rosa and Dr. Belayew and several other laboratories on DUX4, should rapidly increase our knowledge about this mysterious protein and its potential role in FSHD.

Dr. Belayew has support from the FSH Society William R. Lewis, Sr., M.D., and Family Research Endowment Fund; Dr. Hewitt is the recipient of the Delta Railroad Post-doctoral Research Fellowship Award; and Dr. Rosa has held the Society’s Marjorie and Gerald Bronfman Foundation Post-doctoral Research Fellowship Award in the past.

**FSH Society Members: Reach Out to Others through Neurologists**

As more information about FSHD becomes available, as the Society develops more educational materials, and as we anticipate new clinical trials, we are eager to reach more patients with FSHD and to work with their physicians. Patients continue to tell us about their difficulty in reaching a diagnosis.

**Can You Help?**

The Society has developed an introductory letter and package for neurologists positioning the FSH Society as a resource for current information on FSHD as well as providing materials that neurologists can share with patients. We may also mail to neurologists directly, but you are our best ambassadors.

If you would like to have materials to give to your neurologist or other physician that introduce the FSH Society to other patients, contact Jennifer Lazzaro at email: jennifer.lazzaro@fshsociety.org or call (617) 658-7877. You will be assisting patients, their neurologists and other physicians, and you will help to increase the FSH Society’s membership. You will also be helping to make faster progress in research, clinical trials and clinical management.

If you have other ideas about how to reach more patients, or if you would like to have materials to make your own contacts with patients, we can provide them. We need your help in reaching out to people with FSHD while respecting patient confidentiality. The surest way to gain access to clinical trials, new treatments and drugs is if we have a large, organized and reachable constituency.
A New Generation of FSHD Researchers: Individuals with Personal Experience

A Career is Charted: Driven to Help FSHD Through Research

By Sarah Lamb

For years my father’s disease was kept a family secret. Until recently, even his mother-in-law and father-in-law, my maternal grandparents, did not know that my dad has FSHD. Although he faces his disease every day, for a long time he chose not to face it with the community. Nevertheless, with the disease’s progress, this too has slowly changed.

I first became aware of the disease when I was in fourth grade. Not understanding the specifics and knowing that his father died at the age of 40 and other family members had been affected, I became angered at the medical world. Even though my mother worked in a hospital as an R.N., I cringed whenever I saw or set foot in a hospital. Instead, I devoted my time to family, school, and softball. In school, I focused on science as it was the one subject that I never fully understood. When I wasn’t studying, my sister, dad, mom, and I spent our evenings and weekends at the batting cages or on the softball field practicing in between games and tournaments. With time, the daily softball practices outside of the scheduled team practices, ceased as my dad became weaker.

A phone call from my mother during my sophomore year in college reminded me that my father’s condition was not improving. She told me that he had even discontinued duck hunting, one of his favorite activities, as it had become too difficult to hold up his shotgun. With this, I knew I wanted to do something for my dad and other FSHD patients.

Wanting to help support FSHD, I decided to volunteer at a local Muscular Dystrophy Association (MDA) clinic. Organizing pamphlets and flyers, I realized that if I wanted to have an impact on FSHD patients I needed to do something more. At first, I wasn’t sure how I could contribute so I asked around and searched online. Temporarily discouraged by not finding anything, I immersed myself with school. The summer between my sophomore and junior years of college, I was awarded Rockhurst University Deans’ Undergraduate Research Fellowship, and I conducted research with my biology professor, Laura Salem, Ph.D. In my spare time, I volunteered in the emergency room at a local hospital. The challenge of carrying out a research project together with the intensity of social interaction at the hospital temporarily satisfied me.

With the summer behind me, I longed for another research opportunity, but this time I wanted to research something I was deeply and personally interested in FSHD. One afternoon, in the midst of the fall semester of my junior year, I received a pamphlet about Missouri’s Stem Cell Initiative and noticed that the MDA was one of the listed sponsors. Later that evening, I searched online and stumbled across the phone number for the FSH Society. Although I had no idea who I was about to call or what I would or even should say, I picked up the phone and dialed, hoping for some sort of direction. On the receiving end was Daniel Perez. After nervously attempting to explain that I wanted to directly help battle FSHD through research, Mr. Perez advised me to send him a copy of my résumé and, in return, he would distribute it to the laboratories active in FSHD research. His kindness and generosity along with the support of William R. Lewis, Sr., M.D., and the FSH Society were more than I had imagined, and I remain sincerely thankful.

After the completion of my junior year, I was off to work in the laboratory of Michael Kyba, Ph.D., at the University of Texas Southwestern (UTSW) Medical Center at Dallas after receiving UTSW Medical Center’s Summer Undergraduate Research Fellowship. Upon arrival, I was warmly greeted by Dr. Kyba, Rita Perlingeiro, Ph.D., and other members of their labs. Along side two incredible post-docs, Darko Bosnakovski, D.V.M., Ph.D., and Enzi Jiang, Ph.D., and a wonderful technician, Tugba Simsek, I researched a gene likely to play a role in the disease. Although the research was, at times, tedious and frustrating, the positive attitude of the lab members and personal interest were more than enough motivation to continue researching. Likewise, in the beginning, I was at odds as I did not understand why more tests were not being conducted to treat or cure FSHD. However, I quickly became aware that in order to find a cure/treatment, the molecular basis of FSHD must first be understood. Even if my work in the lab only put a small dent in the FSHD research, I am thankful to have been able to contribute, and I am even more thankful to those individuals who study this disease day-in and day-out.

At one time, I worried that there were not any dedicated FSHD researchers. After spending ten weeks in Dr. Kyba’s lab, I no longer worry, but rather I am grateful, thanks to his lab’s teamwork and effort. If anything, I have learned that finding a treatment/cure for FSHD requires dedication, communication, and teamwork—all of which you will find in Dr. Kyba and Dr. Perlingeiro’s labs. I have also learned more of the role of the FSH Society in encouraging and supporting young investigators.

Currently, I am completing my last semester at Rockhurst University and will graduate in May with a Bachelor of Science degree in Biochemistry. I am also in the process of applying to medical schools. My long term goals include providing treatment, guidance, and hope to patients along with researching FSHD.

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Sarah Lamb, recipient of a Summer Undergraduate Research Fellowship at the UTSW Medical Center, together with Dr. Kyba and Dr. Bosnakovski, in the Kyba lab in Dallas, summer 2007.
A New Generation of FSHD Researchers: 
Individuals with Personal Experience

A Career is Charted, continued from page 6

Fortunately, my father has not given in to his disease as he continues to enjoy several activities in his retirement. Although he has given up duck hunting, he still deer hunts and also manages to find miscellaneous projects for my sister and me to take part in whenever I am home for the holidays. As for keeping the disease a secret - that went out the window after I spent my summer researching in Dallas and my dad realized that battling FSHD requires communication and teamwork. 

Two Sides of FSHD

By Ryan Wuebbles

During my 2nd year preliminary exam, while presenting a proposal to create an FSH muscular dystrophy (FSHD) model in the frog Xenopus laevis, I was asked the question “What motivates you to put your time and effort into this project?” The professor, who had been hoping to catch me off guard with this angle of questioning, was surprised when I quickly replied “I am an FSHD patient,” effectively ending that line of questioning. Motivation to help myself and other FSHD patients, and understanding both the challenge of researching this extremely complicated disease and the impact the disease has on individual’s lives gives me a unique perspective on FSHD. I am pleased to share this perspective with the FSH Society.

Having FSHD has shaped many decisions in my life. Its influence ranges from the mundane every day decisions such as stairs versus elevator, or ride versus walk, to the larger choices of living environment, family, and career. In most cases the disease presents boundaries that narrow the number of realistic choices; however, it has positively shaped my choice of career.

I grew up in Livermore California, extremely athletic, playing soccer, basketball and baseball year round. My love of sports continues to this day and is perhaps best exemplified by the fact that at the ages of 10-13 due to overlapping seasons I was involved in two basketball teams and a soccer team for several months, and went to three practices or games a day. I continued sports through high school, and although I managed to make the varsity teams in high school, the disease, though undiagnosed, was beginning to have a profound impact on my strength and abilities. As sports were such a large part of my youth, FSHD taking away my ability to play was particularly difficult for me to deal with in college.

I began college at the University of Illinois (UIUC) planning on pursuing a degree in Electrical Engineering. Two years in, I was diagnosed with FSHD. After struggling with the impact of this diagnosis, I gave up that career track and finished college with a Bachelors of Science degree majoring in chemistry. I knew I wanted to understand FSHD and help FSHD patients like myself, and so I decided to pursue a research track and attend graduate school. In 2002, I began the Ph.D. program at UIUC in cell and developmental biology. Though FSHD has stripped my ability to play most sports, the confidence and work ethic I learned through sports has been channeled into my pursuit of a Ph.D.

My perspective on the FSHD field and motivation as a scientist are a combination of being a patient as well as a FSHD researcher. I joined a lab whose expertise was epigenetics because FSHD pathology is widely considered to stem from disrupted epigenetic regulation. However, the lab uses Xenopus laevis (African clawed frogs) as a model organism so I decided to branch out in my research and investigate FSHD pathology by developing an animal model using frogs. It was my hope that a novel research direction would bring new insights into the disease. However, our lab quickly found out that there was no interest in or funding for generating frogs with FSHD. Even my thesis committee told me this project would not work. I think most Ph.D. students would have followed their committee’s advice and switched projects, opting for a safer, sure thing thesis. Despite this, I believed in our scientific approach and felt the potential advances were worth the risk of failure. Fortunately my stubbornness paid off, the project has proven to be a huge success and I will defend my Ph.D. thesis tentatively titled “Insights from FSHD-like frogs” this spring.

I am not recognized as having FSHD. My 6-foot-4-inch frame, skinny build, facial sparing, and the fact that it is rare to have to squat when meeting people, means most people when meeting me have no idea I have FSHD. I have found the only time this presents a problem is in stores with high shelves, where my height makes me an immediate candidate to ask for assistance getting items down. Interestingly, this also holds true for researchers in the FSHD field. In October, I attended the FSH Society’s International Research Consortium in San Diego, representing a new lab in the research field, where no one recognized me as anything but a researcher. It is an interesting feeling, hiding in plain sight. I was able to view this meeting as both a researcher and a patient. It was exciting to see all the new advances towards understanding FSHD.

As our understanding of FSHD progresses through open-minded research pursuits, we come closer and closer to the ultimate goal of a cure. I’m just glad that I can be a part of it.

Meredith Hanel, Ph.D., Wuebbles’ colleague, is the recipient of the FSH Society Landsman Charitable Trust Post-doctoral Research Fellowship Award.
An Overview of Anesthetic Concerns for Persons Diagnosed with FSHD

By Raymond A. Huml, M.S., D.V.M., R.A.C.

Introduction

I became part of the FSHD family when my daughter was diagnosed with FSHD at Duke University’s Muscular Dystrophy Association Clinic in 2003. Since that time, I have liaised with the officers of the FSH Society, genetic specialists at Duke University and other academic and medical centers in order to better understand the disease and its progression. While I have come to understand that, as yet, we cannot change FSHD genetics or cure FSHD, I do believe that some potentially life-threatening situations for persons with FSHD can be minimized or eliminated.

After a recent trip with my daughter, by ambulance, to an emergency room (ER) for a suspected seizure, I have come to the conclusion that every person with FSHD and their caregivers should be prepared to give details about FSHD and key potential anesthetic complications associated with it, while in the ER, the intensive care unit (ICU) or prior to elective surgery.

This article will explain and examine several key anesthetic concerns for persons with FSHD and is intended to encourage those with FSHD (or their caregivers) to be proactive in providing information about FSHD to those providing medical care. It is not intended to serve as medical advice.

Anesthetic concerns

Even within the high quality medical care system in America, not all medical staff—including nurses, residents, and interns—are familiar with muscular dystrophies and neuromuscular diseases.

• Regarding my recent trip to the ER, it would have been helpful to have a laminated one page description, with websites, available to give to the medical personnel. The FSH Society can also act as a resource in providing information and fact sheets.

The basic anesthetic concern for all persons with neuromuscular diseases, including those with FSHD, is that the respiratory system, due to a weak diaphragm muscle or chronic response to elevated carbon dioxide levels, can be additionally compromised with oral, intravenous or inhaled drugs (or even the inappropriate use of oxygen). For example, muscle relaxants, like valium, can suppress respiratory function by compromising the diaphragm, and opioids (for pain), while not directly affecting the lungs, can have central (i.e., brain) effects that can compromise the respiratory system.

Respiratory insufficiency can occur in all persons with FSHD. However, evaluation of the symptoms and signs of respiratory insufficiency during routine clinic visits is probably more important in patients with moderate to severe FSHD. The first pulmonary visit can be used as a baseline tool; subsequent visits can be used to determine if pulmonary function is changing over time.

• After meeting with a pediatric neurologist with my daughter as a follow-up to the ER visit, I discussed my concerns regarding anesthesia, and we agreed it would be prudent to get a baseline pulmonary function exam.

Regular monitoring of respiratory function is important because insufficiency can occur gradually, over a long period of time without clinical signs. Symptomatic respiratory insufficiency can initially be managed with night time non-invasive pressure support like a BiPAP machine which helps get more air into the lungs. In severe cases, FSHD patients may require the use of invasive mechanical ventilation.

In standard practice, trauma, ER, ICU, surgery and anesthesiology settings, care should be taken not to suppress respiratory drive with narcotics. Oxygen supplementation can be detrimental to patients with hypercarbic (high CO2) respiratory failure and lead to worsening (i.e., higher) carbon dioxide (CO2) levels. Oxygen should generally not be administered unless BiPAP or similar ventilatory support is also being used.

• During the 15 minute ambulance ride to the ER with my daughter, I found it impossible to convince the EMS staff that oxygen supplementation was exacerbating the symptoms—especially since there were no obvious signs of respiratory insufficiency—like increased or labored breathing or blue lips—and normal pulse oximetry readings.

Your physician and pulmonologist can help you periodically monitor CO2 levels in the office or evaluate pulmonary function in the hospital, or even by a nocturnal oxymetry study. The timing for the periodic monitoring of pulmonary function will be determined by the results of the baseline visit, any new clinical signs, you, your pulmonologist and your neurologist may discover.

Elective surgery, surgery for dentistry, or surgery that allows some planning time

Anyone having surgery should be aware of the risks associated with the surgical procedure and/or complications that may arise during and/or after it. While certain risk factors are increased in people with FSHD who undergo anesthesia, each individual is different and reactions to anesthetics may be different. As with all medical procedures, you should talk to your physician about the specifics of your case and what you should anticipate and hopefully have baseline data available for physician review—like pulmonary function data.

The following is a brief description of complications that may occur among people with FSHD who have surgery. continued on page 9
Anesthetic Concerns, continued from page 8

Complications from anesthesia

While this list is not exhaustive, complications in patients with FSHD who have had anesthesia during surgery can include the following:

- respiratory distress,
- rhabdomyolysis (muscle degeneration),
- cardiac complications,
- myotonia (decreased ability to relax the muscles),
- generalized muscle spasms (particularly the jaw muscle), and
- hyper and hypothermia (abnormally high and low body temperature).

Some of these complications appear to be related to the symptoms, severity and stage of FSHD, while other complications, such as respiratory or heart problems, appear to be related to secondary conditions. For example, while rhabdomyolysis appears to be a complication related to NMD symptoms, breathing problems are most often associated with a respiratory problem that is secondary to the muscle weakness caused by the disease process. There are no definitive ways to completely alleviate all risks; however, there are several precautions, like pre-operative testing, that physicians can take to lessen the likelihood of these complications.

Pre-operative testing

One way to prevent or alleviate complications from surgery in individuals with FSHD is through pre-operative testing. These tests may or may not be done based upon the information already contained in your medical records (i.e., symptoms and severity, whether or not you are known to have heart or respiratory problems, etc.). If your physician does not have sufficient information, she/he may run a variety of tests (see below for examples of pre-operative tests) to determine:

- what types of anesthetics to use (i.e., local vs. regional vs. general),
- what drug combination to use for anesthesia, and
- what types of pre- and post-operative measures should be taken to lessen the likelihood of complications.

For patients with FSHD who have not had these tests performed earlier, these pre-operative tests are recommended:

- baseline pulmonary function testing,
- baseline neurologic testing (clinical or diagnostic like EEG), and
- baseline cardiac testing such as an electrocardiogram (ECG).

Identification of a potential problem to medical persons

Without a caregiver present or the ability to speak coherently, medical personnel may not know that you have FSHD. FSHD patients should take care with their advanced medical directives and health care proxies to be sure that the “do not resuscitate clause” does not put them at risk.

Use of a bracelet, necklace, etc., from MedicAlert (or a similar service) will notify medical personnel to potential problems associated with FSHD. A USB flash memory drive with medical files (in PDF or MS Word formats) is an alternative way to transport medical information in a purse or pocket.

On the other hand, use of a bracelet or necklace in adolescents can be problematic because, at this age, it identifies the person afflicted with FSHD to a non-targeted (e.g., non-medical) audience. It may be possible, in lieu of a bracelet, to carry such identification card in the wallet or purse.

Conclusions

- Not all medical personnel are well-informed about FSHD or may not know that you have FSHD unless it is communicated to them either verbally or via a MedicAlert-type device.
- Persons with FSHD manifest a wide variety of clinical symptoms of the disease.
- There are some complications of anesthesia that are more prevalent amongst people diagnosed with moderate or severe FSHD.
- You and your caregiver should be an informed participant in any surgical procedure.
- It is prudent to learn more about the respiratory implications of anesthetics before they become a problem.
- Being aware of the potential complications that may be associated with the use of anesthesia with FSHD and discussing the risks and benefits with your physician before choosing a particular procedure is the best way to prepare for surgery or an emergency room visit and to keep risk at a minimum.
- Review estate planning documents to insure that they are consistent with the medical intervention you wish to receive if you are unable to communicate.

References:

2. Halsall and Ellis. Anesthetics, Academic Unit of Anesthesia, St. James University Hospital, Leeds, The United Kingdom, FSH Watch, Spring 1998.
5. Personal communication, Abresch, RT. Director of Research, Center for Neuromuscular Disease at UC Davis, Davis, CA, 2007.

Editor’s note:

This parent raises important concerns especially in his call for more information to provide medical personnel. The FSH Society will prepare a fact sheet to be carried by patients and their families.
International Research Consortium in San Diego, October 2007

The annual FSH Society International Research Consortium (IRC) workshop was held in San Diego on October 23, 2007. The FSH Society FSHD IRC is a satellite event to the American Society of Human Genetics (ASHG) Annual Meeting. Approximately sixty researchers from around the world attended to discuss FSHD research and solutions for FSHD, despite the adverse conditions of fires raging in San Diego County.

The presence of these investigators and the platform presentations is validating evidence to the community of rapid developments on numerous fronts in FSHD. We are seeing increasing momentum in basic and clinical research initiatives as well as the development of promising, potential treatments for FSHD and other muscular dystrophies. Additionally, there is an increase in government, non-profit, and private funding and in international collaboration of volunteer health agencies and FSHD patients.

Some of the highlights of the 16 presentations and 5 poster presentations were:

A revival of DUX4 was shared; evidence of slowly uncovering the function of FSHD Region Gene 1 (FRG1) was documented; and important clinical studies were covered.

Substantial evidence was presented that FSHD may be considered as a “chromatin disease” and the consortium was educated on new genetic developments in 4q-linked FSHD and non-4q-linked FSHD.

The day concluded with a roundtable discussion about the future of FSHD investigations. Individuals offered a number of observations about future directions and focus: the need for good muscle cells for research, consideration of retinal vascular studies, more attention to the translational character of studies, the desire for pre-clinical and clinical developmental markers, reality of the political landscape of the study of various genes, the continuing need for a natural history of the disease and a means of stratifying patients for trials, an FSH Society website for researchers, and a call for more resources. This was a lively and productive discussion in which FSHD issues were openly discussed with the objective of a new and better future for patients with FSHD. Researchers unanimously agreed that this was one of the best Society IRC meetings to date.

This meeting was sponsored by the FSH Society, the Association Française contre les Myopathies, the Muscular Dystrophy Association USA and Athena Diagnostics. Silvere van der Maarel, Ph.D., William R. Lewis, Sr., M.D., Rabi Tawil, M.D., and Daniel Paul Perez organized and chaired the meeting.

To review more of the day and abstracts of presentations, please go to www.fshsociety.org for the complete program.

One Lap for the Society:
Tire Rack Cannonball One Lap of America to Raise Funds and Awareness for FSHD

By Jeff Jacobs and Udo Horn

The 25th anniversary running of the Tire Rack Cannonball One Lap of America is set for May 3 through 10, 2008. Jeff Jacobs, whose daughter Lauren was diagnosed with FSHD in late 2005, has been preparing to participate in this event for the past 18 months.

The cars and their drivers leave the Tire Rack Headquarters (Tire Rack is the title sponsor of the event) in South Bend, Indiana, and embark on an estimated 5,000 mile trip through the U.S., stopping at racetracks every day. When they get to the track, the vehicles run two or three timed laps on the track, one car at a time. The cars earn points based on their fastest lap times. After the laps are run, the cars and drivers take off for the next track. If the cars get to the next track too early, they get fined points (for exceeding the speed limit). This procedure is followed for the whole week, at the end of which overall and class winners are determined.

Jeff will drive with Udo Horn, a vintage car enthusiast Jeff has known since 1992, when Jeff moved to Maryland. Udo is one of a select few individuals who continued on page 11
One Lap for the Society, continued from page 10

Jeff and Udo have been preparing a 1970 Camaro which would run in the Vintage/Classic American class in the event. This car has been prepared with safety, comfort, and reliability in mind. In order to finish first, you must first finish!

Promotion:
The car will be towed round trip from Arnold, Maryland, to South Bend in an enclosed trailer which will be a traveling billboard for the FSH Society and FSHD awareness. The car, which is near show quality, will be driven from South Bend for the 5,000 mile trip around the country, and once again it will be promoting awareness of the Society and FSHD.

Donations:
Jeff is asking his friends to make a pledge to the FSH Society based on the estimated 5,000 miles driven during the event—from South Bend through Wisconsin, Iowa, Texas, Louisiana, South Carolina, Virginia, Pennsylvania, and back to South Bend. Gifts will be sent directly to the FSH Society. One Lap supporters may request that their gifts be used where they are most needed by the Society, or they may designate that fulfilled pledges be used for research.

If you would like more information about the One Lap for the FSH Society, please go to the Society’s website.

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FSH Watch Newsletter ■ WINTER 2008

One Lap of America Rules:
Minimum of two drivers per car entered. Vehicle must meet all safety requirements. Vehicle must be legally insured and registered. All motor vehicle laws of states through which the vehicles are driven must be obeyed.

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Jeff and Udo have been preparing a 1970 Camaro which would run in the Vintage/Classic American class in the event. This car has been prepared with safety, comfort, and reliability in mind. In order to finish first, you must first finish!

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February 2008

Dear Friends,
In 2007, the FSH Society concluded our most successful fundraising year ever, raising nearly $825,000 from generous friends like you.

You helped the Society make important progress. Thank you for supporting advances in research, education and outreach, and advocacy.

The study of diseases like facioscapulohumeral muscular dystrophy (FSHD) is one of the leading issues of our time. The field of biomedicine offers more opportunities to enrich human life today than at any time in our history. We are optimistic that the community of FSHD investigators, a remarkable group who have committed their professional lives to understanding how the disease works, is moving rapidly toward treatments for patients and to finding a cure.

The list that follows includes all donors to the FSH Society in 2007. We hope you will continue to support this work by joining the Society again in 2008.

Sincerely,

Nancy Van Zant

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