FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY SOCIETY

FSH Watch

A publication of the Facioscapulohumeral Muscular Dystrophy Society
Connecting the community of patients, families, clinicians and investigators

On vision and FSHD

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University of Sydney, Australia

Facioscapulohumeral muscular dystrophy (FSHD) is rightly thought of as a disease of muscle. As indeed it primarily is. Thankfully, the vast majority of patients do not have any clinical consequences from disease affecting any other tissue. But there is an important corollary. A majority of FSHD patients have an unusual, subclinical and often subtle abnormal patterning (vascular telangiectasis) of the blood vessels at the periphery of the retina, which is in all likelihood a developmental anomaly. The retina curves round the back of the eye, and contains the cells which register light.

As these retinal vascular changes are usually benign, why are they important? Two reasons. The first relates to treatment—for although the telangiectasis (pronounced as tel-an-jee-ek-tuh-sis, chronic dilatation of the capillaries and other small blood vessels) is usually asymptomatic, just occasionally there can be serious leakage from the abnormal blood vessels. When this happens the exudate (fluid that has been released from a tissue or its capillaries) tracks centrally to the eye's more capacious posterior pole, where it can cause the retina to detach from its moorings with loss of sight. It is very important for individuals with FSHD to take special care if significant changes in vision occur.

The second reason relates to what these vascular changes might be telling us about the cause of the muscle disease. What pathogenic factors might the muscle disease and the eye disease have in common? And what additional factor(s) might cause symptomatic eye exudates in some patients?

The 'retinal telangiectasis' in FSHD comprises areas of abnormally sparse and abnormally dilated retinal capillaries, sometimes with small outpouchings called microaneurysms, particularly in the retinal periphery. The presence of vascular abnormalities *per se* is not a cause for alarm, although there are certain situations, as will be discussed below, when it is as well to be alert.

Indeed very few FSHD patients will have any abnormalities visible on standard 'direct ophthalmoscopy,' a technique used to examine the central posterior pole (the back of the eye, usually referring to the retina between the optic disc and the macula). Or even on 'indirect ophthalmoscopy,' a more sophisticated technique which also examines the retinal periphery. Indeed the vascular abnormalities can often only be picked up with specialized fluorescein angiography, which highlights tiny blood vessels. This is a very common technique in retinal diagnostic

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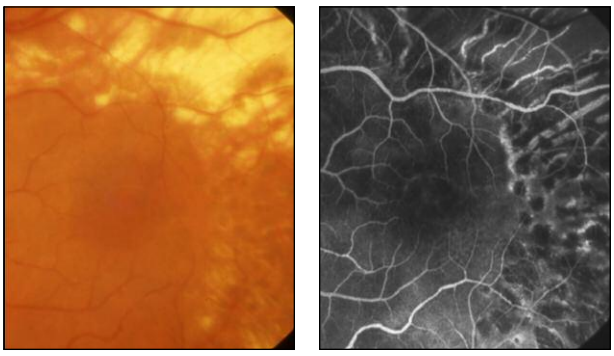

The photograph on the left shows a typical curved exudate at the posterior pole of an FSHD patient who was losing vision in this eye. Vision was substantially restored with laser photocoagulation treatment. The picture on the right is a part of a fluorescein angiogram which shows abnormally patterned blood vessels and microaneurysms, which appear as bright dots.
Courtesy: Moorfields Eye Hospital, London, Professor Alan Bird

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Exercise to improve health and fitness for patients with FSHD

R. Ted Abresch, M.S., Research & Training Center for Neuromuscular Disease
University of California—Davis

At the Research and Training Center in Neuromuscular Disease at the University of California—Davis, we are often asked what type of exercise programs are appropriate for people with FSHD. Although this appears to be a simple question, there is not enough evidence-based information available to give a straight forward exercise prescription.

As everyone knows, there are many potential benefits of strength training and aerobic exercise in healthy subjects. Strength training increases muscle strength and muscle mass and preserves independence. In addition, strength training and aerobic physical activity increases fitness level and capacity for exercise. They also play a role in both primary and secondary prevention of cardiovascular disease—they have been shown to reduce blood pressure, help prevent obesity, and reduce the risk of osteoporosis, arthritis, and type 2 diabetes.

The benefits derived from exercise would certainly be beneficial to individuals with FSHD. We have performed several studies which have shown that subjects with FSHD and other slowly progressive neuromuscular diseases (SP-NMD) have muscle wasting and weakness that limits physical activity and aerobic fitness.

Over the years, the sedentary lifestyle leads to weight gain, additional loss of

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On vision and FSHD, *continued from front page*

medicine: a fluorescent dye is injected into an arm vein, and photographs of the retina are rapidly taken as the dye circulates through the eye before being excreted. That said, unusually tortuous (winding or twisting) retinal blood vessels can be very obvious ophthalmoscopically in some cases of infantile FSHD.

If there are no abnormalities evident on indirect ophthalmoscopy, it is highly unlikely that the vessels will cause any visual problem—and certainly not imminently. Although angiography has been an invaluable research tool in defining the relationship between FSHD and retinal vascular disorders, it is now really only necessary when potentially sight-threatening exudates are seen on ophthalmoscopy, and focused treatment is therefore being considered. It is certainly not routinely recommended in FSHD patients.

The good news is that the retinal exudates can often be successfully treated by targeted laser ablative photocoagulation. In the case of FSHD this treatment might have to be quite 'aggressive' to be successful, but it can prevent or even reverse visual loss if undertaken in a timely way, before permanent nerve fiber damage has occurred. Although it is a very rare complication of FSHD, the fact that it is treatable means that timely detection of sight-threatening exudates is important. Although patients with severe 'infantile onset' FSHD seem peculiarly susceptible to clinical 'Coats Syndrome' (as they are to clinical deafness), no age group is entirely exempt.

Although retinal telangiectasis seems to be a general association of FSHD, there may even be some predisposition to clinically severe retinal disease in certain FSHD families, so if one FSHD patient has needed treatment, experience suggests that it is important for their relatives with FSHD to be especially alert to visual complications.

It is perhaps not surprising then that many of the papers reporting cases of FSHD with retinal complications are in the ophthalmological literature, where they are not necessarily always seen by neurologists. Indeed, the known association between Coats' Disease or Syndrome and FSHD has alerted ophthalmologists to check for signs of FSHD (such as facial weakness) when they see children with Coats' Disease. Sometimes blindness in one eye due to Coats' Disease in infantile FSHD has prompted successful laser treatment to stop the leakage and preserve vision in the other eye. Because of the relative rarity of visual loss in FSHD and because single case reports may not make it to the medical literature, it is likely that the overall prevalence of this complication will be underestimated.

Because visual loss is such a rare (albeit very real, and treatable) complication of FSHD, there are legitimate different clinical viewpoints about the implications for visual screening. My personal viewpoint is that precisely because it is treatable and devastating, it is worthwhile undertaking simple and non-invasive ophthalmological screening procedures of individuals, particularly young children who may not complain of visual loss, even if they are at very low risk. There are some U.S. clinicians who advise retinal ophthalmoscopic examination under anaesthetic of very young infants who present with facial weakness who might have FSHD. And of course infants will not be able to complain of losing sight. Adults and older children need simply to be advised to report visual symptoms immediately.

Parents of children at genetic risk of FSHD should be aware that occasionally the eye disease presents before the muscle disease, even if this is more typically seen in 'sporadic' FSHD.

The abnormal retina vascular pattern in FSHD is identical to that which otherwise occurs in Coats' Disease, which is usually a unilateral disease of young boys. Semantic purists often prefer the term Coats Syndrome when this retinal disorder occurs in other contexts (such as FSHD). In turn, Coats' Disease is part of a group of developmental retinal vascular disorders with identical or virtually identical patterns of peripheral retinal blood vessel abnormalities and which can be due to mutations affecting one of several components of a signaling pathway (known as 'Wnt').

'Wnts' are secreted glycoproteins which act on the cell membrane and

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Letter from the chairman, board of directors, FSH Society

October 2008

Dear Friends,

I had the great privilege of attending the ribbon cutting and official opening of the Wellstone Center in Watertown, Massachusetts, on October 10. I know you share my excitement and that of my family: today there is a research center focused on facioscapulohumeral muscular dystrophy (FSHD).

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

The FSH Society has a pivotal opportunity today, to provide gifts for additional projects that will lead to more research discovery. Your gifts will also enable us to continue our longstanding support of multifaceted FSHD research not included in the Wellstone program.

The new center brings us closer than ever to the development of a treatment for FSHD. You and your fellow FSH Society members have contributed to this progress to date. I hope you will continue to support these advances and give another gift at this time.

Thank you very much.

Sincerely,

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

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It is the editorial policy to report on developments regarding FacioScapuloHumeral Muscular Dystrophy (FSHD), but not to endorse any of the drugs or treatments discussed. We urge you to consult with your own physician about the procedures mentioned.

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www.fshsociety.org

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Dr. Lewis and other Society members enjoyed this event:

Boston Biomedical Research Institute
and Facioscapulohumeral Muscular Dystrophy Society
invite you to

NEW ENGLAND'S FIRST
SENATOR WELLSTONE MUSCULAR DYSTROPHY
COOPERATIVE RESEARCH CENTER

BIOMARKERS FOR THERAPY OF FSHD

FRIDAY, OCTOBER 10, 2008
4–6PM

Boston Biomedical Research Institute
64 Grove Street • Watertown, MA

WELCOME
Charles Emerson, Jr., Ph.D., *Director*
and Louis Kunkel, Ph.D., *Co-Director*
Wellstone MD CRC for FSHD

PATIENT PERSPECTIVES ON THE WELLSTONE
Mr. Stuart Lai and Mr. Justin Cohen
FSHD patients and members of the FSH Society, Inc.

RIBBON CUTTING
Daniel Perez
President and CEO, FSH Society, Inc.

Enjoy cocktails and hearty hors d'oeuvres

Kindly reply to Lisa John at 617-658-7799
or email at ljohn@bbri.org

Boston Biomedical Research Institute

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Exercise to improve health and fitness, continued from front page

muscle mass, diminished walking endurance, increased fatigue and pain. As a result, individuals with FSHD and other SP-NMDs have significantly higher risk factors for metabolic syndrome (the combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes) and chronic disease resulting from obesity and a sedentary lifestyle.

Unfortunately, even FSHD subjects with normal weight and body mass indices also have problems with increased body fat. A recent study by Andrew Skalsky, M.D., in our Center revealed FSHD subjects had 14% less lean muscle tissue in their trunk, but 76% more fat in the trunk than an age-, weight-, and height-matched control group. In addition, the FSHD subjects significantly lost muscle mass and had a concomitant increase in fat mass as they aged, which was not seen in the control population. We don't know if these changes further increase the risk for metabolic syndrome for individuals with FSHD. We also do not know whether these risks can be reversed with strengthening exercise or increased physical activity. No well-controlled studies have been performed that can answer these questions.

If there are so many benefits to physical activity, why haven't doctors prescribed exercise for FSHD patients? It is because physicians have been concerned that exercise might cause overwork weakness in patients with SP-NMDs. Back in the 1950s, during the last of the polio epidemics, there were a series of reports that showed that patients who were recovering from acute polio got significantly weaker after they had started exercising. These studies raised an alarm—physicians reacted by telling their patients to limit exercise because strenuous exercise could put patients back in a wheelchair.

These concepts were further reinforced by studies that showed that individuals with Duchenne muscular dystrophy had the greatest muscle degeneration in muscles used during sustained physical activity. Other reports showed that individuals with FSHD who carried heavy loads during work or performed unsupervised weightlifting had increased weakness in the arms on their dominant side as compared to their non-dominant side. The researchers hypothesized that the observed weakness that was evident in the dominant limb was caused by the extra stress from overwork injuries as a result of extra stress placed on the dominant limb. As a result, most physicians when asked about exercise for their patients with FSHD say things like, "Don't over do it, and be very gentle" or "Go sub-maximal and use very low resistance." Patients do not know how to interpret this advice, and more often than not, they do not want to do anything. As a result patients become sedentary and deconditioned, which leads to additional muscle loss from disuse and increased levels of obesity.

So where does this leave us now? What type and intensity of exercise may be beneficial and what types are detrimental for patients with FSHD? About ten years ago investigators from

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On vision and FSHD, continued from page 2

thence via a highly complex series of interacting 'signals' to control the nuclear transcription of genes for other proteins, especially during development. Wnt signaling is crucial in the development of both muscle and the retina and its blood vessels—as well as in muscle regeneration and in many other tissues.

Most cases of Coats' Disease are idiopathic—meaning we do not know the cause. But some are due to mutation of 'norrin,' a Wnt activator, which is also mutated in Norrie Disease, a much more severe and X-linked disorder of infants. Norrin mutation also causes yet another inherited vascular disorder, familial exudative vitreoretinopathy (FEVR). FEVR can also be caused by mutations for genes of other proteins in the Wnt pathway, called 'frizzled 4' and lipoprotein related protein 5 (LPRP5). Quite clearly, FSHD is not due to any of these three proteins, but it will be important to consider whether some other crucial component in Wnt signaling might be affected in FSHD. This is especially so given that Wnt proteins interact with members of the PITX family during developmental patterning and that Wnt pathways also play a critical role in the development of muscle tissue and in the differentiation of the 'satellite cells,' from which muscle regenerates in adult life.

There was a certain focused serendipity about the discovery of retinal vascular abnormalities in FSHD. Whereas there had been occasional reports of eyes being enucleated (removed) because of Coats' Disease in children with FSHD, there had been no consideration of the broader implications. But Coats' Disease is known to be due to leakage from small blood vessels. So when I was working at Hammersmith Hospital in London and saw a patient with a retinal scar which had been attributed to infection with toxoplasmosis, I wondered whether it might instead actually be due to leakage from blood vessels, and if that were the case whether her other visually asymptomatic FSHD relatives might also have abnormal retinal blood vessels. So I collaborated with Professor Alan Bird and Dr. Eric Gurwin at Moorfields Eye Hospital in London. When 'fluoresceins' showed that all four FSHD affected members of that family had abnormal peripheral retinal blood vessels, we decided to undertake a formal research study of FSHD patients at The National Hospital for Neurology in London. Our study which showed that a majority of patients had demonstrable, albeit often subtle, peripheral retinal vascular changes was later confirmed by Professor George Padberg's group in Leiden.

It is also important to bear in mind that early-onset FSHD can be associated with clinical hearing impairment; and, if the general clinician is not very alert, the absence of facial expression combined with hearing loss can sometimes lead to a misdiagnosis of mental retardation.

FSHD patients/families that have had visual complications of FSHD are invited to contact the FSH Society or the author, who is interested in collecting experiences of FSHD retinal complications for compilation.

Dr. Fitzsimons can be reached at rfitzsim@mail.usyd.edu.au ✧

Exercise to improve health and fitness, *continued from page 4*

our Center examined the effect of a moderate resistance, home-based strengthening exercise program on 27 people with FSHD and other SP-NMDs. During the first week of a 12-week exercise program the patients were instructed to strengthen their knee extensors by performing three sets of four repetitions and at 30% of their maximum strength, which is pretty low for that muscle. The subjects gradually increased their exercise regimen and by week 12, they were performing three sets of eight repetitions at 40% of their maximal strength. Even though this exercise regimen was very moderate, it was enough to produce a significant increase in strength. However, subjects who had less than 15% normal strength were unable to get any strength gains from strengthening exercise. Because we found improvements in a moderate resistance program, we wanted to see if we could get greater effects with a maximum resistance exercise training program. The subjects didn't get any stronger compared to the group who performed the moderate exercise. Therefore, we recommend against high resistance exercise for individuals with FSHD.

A recent study by E. L. van der Kooi *et al*, in the Netherlands, (see the Cochrane Reviews) also reported that moderate-intensity exercise strength training appears to do no harm in patients with muscle disease, but there is insufficient evidence to show that it increases strength. Nevertheless, there is some work that suggests that moderate aerobic training programs might improve fitness and reduce the risks associated with obesity and inactivity in FSHD patients. Most aerobic training programs have demonstrated that individuals with FSHD have similar beneficial cardio respiratory adaptations to sub maximal aerobic exercise training as able-bodied persons.

Investigators from our Center performed a 12-week home-based aerobic walking program in subjects with FSHD and other SP-NMDs. Although we did not see any improvements in their fitness (no change in peak VO2, a key measure of your body's exercise potential), we did find that SP-NMD patients had some beneficial effects, including a reduction in heart rate and systolic blood pressure. Recently, we performed a study to determine whether a 6-month home-based activity and dietary intervention can increase activity level, reduce caloric intake, and impact positively components of metabolic syndrome. The FSHD and other SP-NMD subjects increased their activity by 27% above their baseline value, significantly reduced their body fat percentage and decreased their caloric intake over 300kcal/d (the calories referred to in diet and exercise). However, this exercise regimen did not reduce the risk factors associated with metabolic syndrome.

Although the direct benefits of exercise have not been proven scientifically, there are many other potential benefits from exercise, such as restoring energy and reducing fatigue. Exercise has been shown to reduce depression, increase self-esteem, reduce pain and reduce social isolation and loneliness. Based on these results, we recommend that patients with FSHD perform moderate strength training and regular aerobic exercise to maintain cardiovascular fitness. Studies with longer duration are needed to assess the long-term effects of training on disease progression in patients with FSHD. The general exercise recommendations that we suggest for individuals with FSHD are listed below and were adapted from a consensus conference of experts (Fowler *et al* Am J Phys Med Rehabil 2002:81 (Suppl):S187-S195).

- Adopt an active lifestyle for its physical and psychological benefits.
- Perform moderate-intensity resistive strengthening exercise during the early stages of the disorder in muscles that have antigravity or greater strength. High intensity exercises should be avoided.
- Perform moderate-intensity aerobic training programs to maintain or improve aerobic capacity.
- Individuals will have a variable response to training depending upon their degree of weakness and fatigue, their rate of progression, and their level of conditioning.
- Stretching and range-of-motion exercises may be helpful in decreasing the discomfort attributable to the limited mobility of the joints secondary to muscle weakness. ✧

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These exercise recommendations come from the National Center on Physical Activity and Disability (NCPAD). The mission of the NCPAD is to promote substantial health benefits that can be gained from participating in regular physical activity.

Important considerations before exercising

- Obtain a complete medical evaluation and physician consent before beginning an exercise program.
- Work with your cardiologist to determine cardiovascular complications, such as cardiac arrhythmias, congestive heart failure, and right and left ventricular dilation which may limit your ability to exercise or the intensity at which you exercise.
- Obtain a specialized prescription for spinal deformities, such as scoliosis, kyphoscoliosis and lordosis.
- Respiratory problems: be aware of possible complications associated with weakness in the respiratory muscles.
- If you experience exercise-related cramps or fatigue, rest and decrease intensity.
- Log your daily activities so that you can determine the appropriate intensity for your exercise program.
- Set reasonable goals with activities that are fun and game-oriented.
- Nutritional counseling coupled with the exercise program will help prevent weight gain.

Cardiovascular training guidelines

- Set an exercise pace that feels good to you. Rate your level of exertion by the Rating of Perceived Exertion scale (range of 6 to 20 where 6 = very light, and

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20 = very, very hard); 12 to 14 is a good target zone.
- Focus on the duration, rather than the intensity of your workout.
- Engage in brief walking sessions (20 to 30 meters) several times daily, to increase cardiovascular endurance. The walking surface must be level.
- Perform exercises that utilize multiple, rather than single, muscle groups.

Types of cardiovascular training:

Arm and leg ergometry; walking, cycling, swimming.

Strength training guidelines

- Strength training should help you retain strength in your arms, shoulders, legs, and hips. Your balance and trunk stability can indicate the preferred type of strengthening program.
- Splints or braces can assist in a strengthening program if you experience muscle weakness or atrophy.
- If possible, perform multi-joint rather than single-joint exercises.
- Note that it may be necessary to limit your use of weights so that you have energy left over for other tasks.
- Focus on increasing the number of repetitions rather than increasing the weight. Do not use the overload principle.
- If you do use weights, utilize light weights or no resistance. Begin with one set of five to 10 repetitions, and work up to three sets of eight to 12 repetitions, three sessions per week.
- Do not strength-train the same muscle groups on consecutive days.

Types of strength training:

Weight machines; dynamometer for grip strength or back/leg strength; theraband (elastic resistance bands).

Flexibility training guidelines

- The goal of flexibility training is to improve range of motion, balance and coordination.
- Perform a complete warm-up and cool down stretching program before and after each exercise program. Ideally, stretches should be held for 10 to 30 seconds, repeated three times, and performed three to four times daily.
- Focus on main muscle groups, especially those more likely to develop contractures, such as those in your arms, wrists, fingers, shoulders, legs, and hips.
- Perform all stretches in a fluid manner.
- AVOID overstretching or hypermobility.

Types of flexibility training:

Active stretches-stretches you perform on your own; passive stretches-stretches someone helps you perform.

Note: The information provided here is offered as a service only. The National Center on Physical Activity and Disability, University of Illinois at Chicago, the National Center on Accessibility, and the Rehabilitation Institute of Chicago do not formally recommend or endorse the equipment listed. As with any products or services, consumers should investigate and determine on their own which equipment best fits their needs and budget.

National Center on Physical Activity and Disability: http://www.ncpad.org ✧

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Gifts of stock to the FSH Society

As you begin to review your financial affairs as 2008 draws to a close, it will be important for you to consider whether investment market conditions make it advantageous for you to make a gift of stock to the FSH Society at this time.

Consider the tax benefits

A gift of appreciated securities held for more than one year may provide significant benefits to you as a contributor, such as:

- Providing you a charitable income tax deduction for the fair market value of the gifted securities as of the date of gift.
- Eliminating capital gains tax that would ordinarily become due if you had sold the appreciated securities on the open market and donated the proceeds from the sale to charity.
- Claiming your charitable deduction against up to 30% of your adjusted gross income. Any unused deductions can be carried forward over the next five years.
- Providing a way to help you to achieve your long-term financial objective of reducing your income and estate taxes.

Caution—Tax benefits are lost if:

- *the stock is sold and then proceeds given;*
- *the stock is worth less than you paid for it;*
- *the stock has been held for one year or less.*

For more information, contact the FSH Society at (617) 658-7878, or go to the website, www.fshsociety.org and click on Contribute and Gifts of Stock. You should also consult with your financial advisor before initiating a charitable gift of stock. ✧

Charitable IRA Rollover opportunity

On Friday, October 3, Congress approved and the President signed legislation that includes the immediate and retroactive extension of the popular Pension Protection Act of 2006 provision which allows taxpayers over 70-1/2 to make tax-free distributions from their traditional and Roth IRAs (Individual Retirement Accounts) directly to charity in 2008 and 2009.

Check with your advisors about the best ways to take advantage of this opportunity to give to the FSH Society. As always, the FSH Society will also be pleased to assist you in any way possible. ✧

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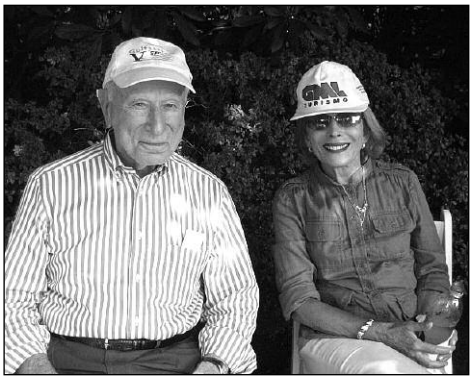
The FSH Society would like to thank you for your support as we carry on the fight for excellent research, treatment and a cure. We cannot do it without you!

FSH Society members and friends have a picnic in New York

Ken and Judy Seslowe with Beth Johnston

Snow cones!



Sandy Batkin and Rosalind Devon

The picnic netted $37,000 for a new post-doctoral research fellowship.

On September 14, a beautiful day by the Long Island Sound in Mamaroneck, New York, FSH Society member, Beth Johnston and a very energetic committee held a family picnic to raise funds for FSHD.

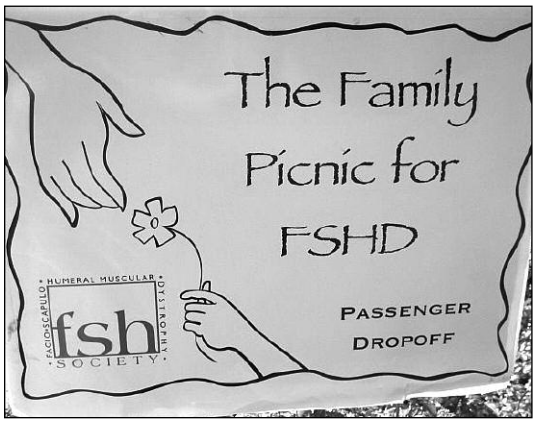
Early in the summer, Beth gathered a group of FSH Society members, family members and friends, to plan the picnic. Judy and Ken Seslowe graciously offered their home and gardens for the event, and work began.

By Sunday, September 14, over 150 adults had purchased tickets for themselves and 100 children! Dozens more individuals could not attend but sent contributions. Everyone enjoyed box lunches or a table of special food including snow cones for children. A silent auction entertained adults, while children were occupied with wandering through a maze. Clowns and face painters also entertained them.

Special thanks to Beth, her husband Jeff, and other volunteers who served on the committee: Carrie Baumgartner, Kari McGovern, Jamie Seslowe, Emily Rosenfeld, Susannah Van Dyke, Debbie Younger, David Younger, Deborah Schwartz, and some great Girl Scouts who want to help again in 2009! Beth is already planning for next year.

The picnic netted $37,000 for a new post-doctoral research fellowship.

Thanks to Alisa Dornau and Jennifer Egert for photos. ✧



Jeff and Beth Johnston

Auction

Face painting

Tenth Biennial International Patient and Researcher Network Meeting brings people from near and far to Iowa

In late July, nearly 130 people gathered in Coralville, Iowa, for the FSH Society's tenth biennial Patient and Researcher Network Meeting. Young people and young families joined us in greater numbers than before, as did people from Iowa, Minnesota, Kansas, Wisconsin, Nebraska, Missouri, Illinois, Michigan, North Dakota, and Texas. Old friends returned and new friends also arrived from California, New Jersey, Maryland, Florida, Ohio, Virginia, Kentucky, Mississippi, Arizona, North Carolina, and New York. Everyone welcomed attenders from France, Australia, and Canada.

We had great concern for our friends in Iowa when the area experienced floods in June. Although many people experienced much personal and economic hardship, eastern Iowa recovered to a reasonable point for this and other conferences by late July.

The 2008 conference program was well circulated in advance and is not repeated here. It added a dimension for teenagers and young adults by way of two workshops in the afternoon sessions. In addition to making the meeting more accessible to midwesterners, we selected this location so that families and children with infantile FSHD could participate in the clinic offered by Katherine Mathews, M.D., and staff, on Monday, following the meeting.

Evaluation

Attenders evaluated their experience at the meeting. Overall they were quite positive, and they offer the Society good advice for the future:

- They were most appreciative of the opportunity to meet others like themselves.
- They sometimes found the presentations too technical, and they wished for copies of the presentations in advance.
- They suggested spreading the meeting out over 2-3 days.
- They would like more practical information about disease management.
- They suggested that we offer more age segmentation in organizing the program.
- They liked the convenient and less expensive location. (Of course, the latter does not allow for opinion for non-attenders who did not like the location!)

Future meetings

The next meeting will be in the latter half of 2010. The Society will attempt to respond to the good suggestions that we heard. Especially, we will work to expand the meeting, perhaps with optional sessions the day before and the day after the core program, and we will try to increase demographic segmentation in the programming. We will also continue to listen to your ideas for the future. Perhaps early in 2009, we will give you an opportunity to vote for the region of the country where the 2010 meeting will be held.

Special thanks to the clinicians and researchers who provided our program and to the great staff at the University of Iowa Hospitals and Clinic.

Louis Kunkel, Ph.D., and panel of speakers

William R. Lewis, Sr., M.D., chairman of the FSH Society Board of Directors, opens patient/researcher network meeting on July 27

Teenagers and young adults workshop

Thanks to Leslie Berkeley for photos.

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Save the Date

A Festive Evening of Music and Song

March 25, 2009

Concert and Silent Auction to benefit the FSH Society

Merkin Concert Hall at Kaufman Center, New York. For more information, go to www.fshsociety.org

FSH Society members plan gatherings for 2009:

- Hobe Sound, Florida—Sunday afternoon—February 2009
- Los Angeles area—Brunch—Spring 2009
- Denver—Reception—Spring 2009
- Cape Cod—Fundraising Walk—Summer 2009 ✧

International Patient and Researcher Network Meeting

Parents Michelle and John Hosp share their search—for information, for other families and for coping skills

Preparing for our first trip to the FSH Society conference in Iowa City was nerve-racking. It was obviously not a pleasure vacation but rather a painful journey to gain more information and find more people like us. People like us would include families with small children with infantile FSHD. In our case our son is three, so the need to know more and talk to people who "get it" was our driving force.

The night before the conference we found ourselves explaining to our three year old that you are going to see people using wheelchairs and some people that may not be able to smile back when you say "hello." We tried to use the opportunity to talk about different ways people get around and that people often smile on the inside, even if we cannot see it on their faces. As we tried to prepare him for the experience we realized it was just as much a preparation for ourselves.

After registering, we started searching for other families with small children. We met an amazing family with another three year old and would meet more families with young children. While our stories are different in relation to age when our children were diagnosed, how they are progressing related to issues around FSHD, it is a relief to know we are not alone. Just talking to someone, even for five minutes, who "gets it," is an unbelievably comforting experience.

The start of the conference entailed presentations made to the entire group. The presentations were helpful for us since we are new to the world of FSHD. It was information that I know is available somewhere, but to have the experts reviewing it and answering questions made it more accessible. Somehow sitting in a room with over 100 other people who can relate on some level with what you are dealing with made it seem less frightening.

"The FSH Society conference provided the much-needed information about the specifics of infantile FSHD plus provided a personal network to talk to other families who understand, even if we at times do not understand."

—Michelle & John Hosp

One of the sessions we attended for caregivers and friends of people with FSHD was also very helpful. As we went around the room and introduced ourselves we couldn't hold back and boldly stated "We don't want to be here. And really, this sucks." We went on to say that while we are starting to learn to be okay with it, we need the space to voice our fears, disappointments, and pain. As we looked around the room and noticed nods from others again we realized we are not alone. Hearing how other families are coping and have been coping gave us much needed reassurance we will be able to handle it (whatever it is), and in time it will be okay.

For us the greatest fear is not having the right information and contacts. The FSH Society conference provided the much-needed information about the specifics of infantile FSHD plus provided a personal network to talk to other families who understand, even if we at times do not understand. We are looking forward to going back and would encourage others to do the same.

Stephanie O'Meara, freshman, Creighton University, on taking a big step

The most memorable part of the FSH Society conference was the people I met. I cannot even remember what the presentations were on but I can remember every interaction I had with the people at the conference. The first person to introduce herself to me was a young girl. She was no older than five with the cutest smile and a mouth that did not stop. She was followed closely behind by her younger sister who was clearly affected by the disease. As the younger sister ran towards us she stumbled and fell but quickly picked herself up and continued running like nothing had happened. I was stunned to see such perseverance in such a young child. When she got to us, she entered our conversation as any 3 year old would. The two sisters jabbered on about who knows what while I stood there

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Patients and researchers assembled in Coralville, Iowa

Conference attenders & friend

International Patient and Researcher Network Meeting, *continued from page 9*

utterly amazed by these two young girls. One was affected by a disease but did not let it get in the way of what she wanted to do and the other would be the first one to her sister's side if she needed help.

During the session I led, a session for teens with FSHD, I met the most amazing teenagers in my life. Each one of them had their own stories and weren't afraid to share them. I may have started the session leading, but by the end we were just a group of friends sharing our experiences. There was a girl, a year older than me, whom I immediately clicked with. She shared her problems and listened to mine. With me beginning my freshman year she gave me hope and courage to begin a new experience. We still keep in touch through email today, and I know that she will always be there for me if I need her. Then there is the girl who is a couple years younger than me who makes me laugh till my sides hurt. She shows me that, yeah having the disease is hard but it is just a tiny aspect of our lives. And it is great to be able to share my wisdom with her to make her high school years the best. Although we just recently reconnected, it is like we were never apart. These are just a few of the people who influenced my life during that session.

"The FSH Society conference changed my life. I met the greatest people. They knew what I was going through and were eager to help. I was known as 'the girl who is starting Creighton in the fall' to the adults, a friend to the people my age, and a person to look up to for the children. I may be all those things to those people, but they have no idea how much they influenced me. Over the course of a couple days, I gained hope, friendship, and an experience I will never forget."

—Stephanie O'Meara

I guess what I am getting at is that the FSH Society conference changed my life. I met the greatest people. They knew what I was going through and were eager to help. I was known as "the girl who is starting Creighton in the fall" to the adults, a friend to the people my age, and a person to look up to for the children. I may be all those things to those people, but they have no idea how much they influenced me. Over the course of a couple days, I gained hope, friendship, and an experience I will never forget.

Sixto Garcia, soon to become a junior at the University of California, Northridge

The Garcia family enjoyed immensely the Iowa conference. First, having participated in the Boston conference two years earlier, we touched base with old friends and more importantly, met new ones! Second, the organization of the meeting was much more fluid, informative, and it was well managed.

I am 21 years old, and still in my prime of developing a personality; being with others who may feel, look, and experience as I do is a key ingredient in being able to not only cope with FSHD but also to adapt and live with it. In my first conference I was struck by the varying and many people that I could relate to. Their experiences, feelings, and outlooks in life made me feel very welcomed.

I came to the Iowa conference more prepared than I arrived at the Boston conference, as I knew I would see familiar faces. But this time, my goal was not just to find a place to fit in, but also to help others find what I found. I have learned a lot from the first conference and from the 2 years since then; as a psychology major, I felt the obligation to motivate those who were in my position at the first conference.

"Life is just an adaptation of obstacles. I now see that life is beautiful and regardless of FSHD. I don't think I would be the passionate, intelligent, sensible, and motivational person that I am today. I have left with my head held high."

—Sixto Garcia

I want everyone to know that not only is the conference a great experience, but a necessity if you want to cope and adapt with FSHD. I am fortunate to be someone who is mildly affected by FSHD, and seeing those less fortunate, and speaking with them on how they conduct their own lives with FSHD not only showed me what I still have, but what I should do to maintain it. I have heard stories and strategies on how to begin dealing with FSHD, but nothing is more provocative than seeing and speaking with a person that can tell you just how far FSHD can go. Looking into their eyes and seeing them smile when a young person comes up and asks them for knowledge is a priceless experience. And what I've learned from studying psychology is that the best way to overcome an illness or disadvantage in life is to help those affected. I saw that those I conversed with at the conference felt needed, and that may be a change from their daily life of feeling dependent on others.

I wish all those I spoke with the best of luck and I truly admire everyone's strength by showing up to either one of the conferences. I hope to see you all again soon. Life is just an adaptation of obstacles. I now see that life is beautiful and regardless of FSHD. I don't think I would be the passionate, intelligent, sensible, and motivational person that I am today. I have left with my head held high. Thank you to the FSH Society to make this wonderful conference possible! ✧

FSH Society Research Fellowships yielding fast forward dividends and insights

Research summary

FSH Society research fellow, Kyoko Yokomori, Ph.D., is studying a complex involved with D4Z4 (the FSHD area at the end of chromosome 4) that normally modifies histones (proteins) at D4Z4 and recruits factors that are involved in gene silencing. Dr. Yokomori and her colleagues believe that this complex bound to D4Z4 spreads its silencing effect to target gene(s) by long-distance interactions. In FSHD, this process is disrupted and the silencing is lost when only one strand of the chromosome is shortened. In addition, FSHD patients who are clinically affected, but who do not have a deletion on chromosome 4, e.g., the non-4q-linked variety, are found to have a disruption of this complex and the silencing is again lost. Patients with four other dystrophies do not experience this particular over expression and the loss of gene silencing.

Further, this lab has also found that this disrupted complex causes over expression of Pitx2, thought to be one of the target genes in FSHD. They have found that artificial over expression of Pitx2 in muscle cells leads to the increase of another gene, known to be highly over expressed in FSHD patient muscles, called Pitx1. (This is the work of Yi-Wen Chen, D.V.M., Ph.D., also funded by the FSH Society.) Pitx1 over expression was found to cause muscle atrophy. Thus, the results suggest that the increase of Pitx2 indeed critically contributes to FSHD pathogenesis. If

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Are you a member of the FSH Society? Have you made a gift to the Society in 2008?

The FSH Society is a world leader in combating muscular dystrophy. It has provided $2 million in seed grants to pioneering research worldwide and it has created an international collaborative network of patients and researchers.

If you are not already a member, won't you join in this effort? Please return your membership gift, or another gift, in the envelope enclosed inside this issue of *Watch*.

Or contribute online at:
www.fshsociety.org.

Go to **Contribute**, and select the gift category you wish to make. Thank you! ✧

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Combined Federal Campaign (CFC)— Are you a federal, postal or military employee?

Federal civilian, postal and military personnel can donate to the FSH Society through the Combined Federal Campaign during the campaign season, September 1 to December 15, 2008. **The FSH Society code is #10239.**

For more information about the CFC, you may go to the official website: http://www.opm.gov/CFC/ ✧

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Mary and Man So Lee, M.D., celebrated their 50th wedding anniversary, Staten Island, New York, August 9, 2008.

Above: *Family and friends made gifts totaling more than $30,000 to establish the Aubrie Lee Family Research Fund, to support research in infantile FSHD. The Lees, their five sons and wives, and many grandchildren are pictured above. Aubrie Lee is in the first row, third from the right.*

Left: *Aubrie Lee and her parents invited her friend, Justin Cohen, together with his family to her grandparents' anniversary dinner.*

FSH Society Research Fellowships, *continued from page 11*

the researchers can modulate Pitx2, which is a transcription factor protein, they can also modulate Pitx1 and in turn control and treat FSHD.

Finally, the researchers postulate that Pitx2 is involved in early human development. To study these embryonic effects, Dr. Yokomori is now developing embryonic mice models and human embryonic cell model systems, the next steps in developing a treatment.

A key understanding here is that patients with several other dystrophies do not experience this particular over expression and the loss of gene silencing. It is very interesting that FSHD patients with one strand of the chromosome shortened, as well as the FSHD patients with no shortening of the chromosome, the non-4 linked FSHD cases, do experience this particular over expression and the loss of gene silencing.

Last, this particular histone complex could lead to a new and novel method to diagnostically and genetically test patients with both types of clinically determined FSHD e.g. those with a shortened D4Z4 region (the chromosme-4-linked) and those with no shortening of the D4Z4 region (the non- chromosme-4-linked).

Drs. Ball and Yokomori wrote the following on efforts to find a more rapid and efficient diagnostic and prenatal test for all types of FSHD.

Dr. Yokomori has support from the FSH Society Helen Younger and David Younger Post-doctoral Research Fellowship Award. ✧

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Potential novel diagnostics For FSHD

Alexander R. Ball Jr., Ph.D., and Kyoko Yokomori, Ph.D.
University of California, Irvine, California

Facioscapulohumeral Dystrophy (FSHD) is reported to have a 1 in 20,000 incidence. However, there is great concern that the actual number of affected individuals is significantly higher due to undiagnosed cases (with a likely incidence of 1/7,000). A proper diagnosis of FSHD depends initially on recognition of clinical signs and symptoms and differentiation of FSHD cases from other muscular dystrophies.

Molecular studies have been used to reinforce the clinical impression. The primary approach has been through detection of 4qD4Z4 repeat contraction by pulsed-field gel electrophoresis (PFGE) following restriction digestion. However, this method cannot identify phenotypic FSHD patients who do not have a chromosome 4 repeat contraction, and certain band patterns can prove difficult to interpret. Our work focuses on histones which are the main protein components of chromatin. Histones act as spools around which DNA can wind, and influence and have a role in gene regulation. We have recently discovered a specific change in histone modification at the D4Z4 repeat sequences (known to be associated with the disease) which is detected in both 4q-linked (with D4Z4 repeat contraction) and phenotypic (no repeat contraction) FSHD patient cells.

Importantly, this change is highly specific for FSHD; no significant change of this histone modification was observed in Duchenne muscular dystrophy (DMD), limb-girdle muscular dystrophy (LGMD), oculopharyngeal muscular dystrophy (OPMD), inclusion body myopathy associated with Paget's disease of bone and frontotemporal dementia (IBMPFD), or "immunodeficiency, centromeric instability and facial anomalies" (ICF) syndrome patient cells.

Furthermore, this change is seen not only in affected muscle cells or fibroblasts derived from patient muscle biopsy samples, but also in patient lymphoblasts (derived from blood). This suggests that this histone modification alteration occurs early in development and is therefore found in many cell types in an affected individual. This is potentially very useful from a clinical diagnosis standpoint.

One could envision making a diagnosis of FSHD by analyzing peripheral mononucleocytes that could be obtained significantly less invasively (and less painfully) than muscle biopsy samples. Detection of the histone modification alteration is accomplished by performing a chromatin immunoprecipitation (ChIP) analysis, which entails crosslinking of cellular DNA and immunoprecipitation with antibody specific for a particular histone modification marking. We anticipate that a sufficient number of patient cells could easily be acquired through a standard blood draw. Experiments are currently underway to test this notion. If we can demonstrate that this is the case, ChIP can be used to analyze the histone modification markings in the patients' blood samples for FSHD diagnosis. ✧

Connecting with other FSH Society members

Articles in this issue and recent conversations remind me that many Society members express an interest in meeting others with FSHD. In recent months, many of you have asked if we could help you connect. Consider the following:

- FSHD patient in New Jersey who would like to meet others nearby
- Parents with small children who would like to connect by email or phone
- Los Angeles area members planning a winter or spring brunch
- Teenagers and young adults have formed a virtual network and welcome new friends

If you would like to participate in one of the above, or if you have a networking request, email me, nancy.vanzant@fshsociety.org, with your permission to give your contact information to others, and we will help you connect!

—Nancy Van Zant

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