Synapse

Volume 19, Issue 3 Fall 2016

Newsletter of the Spastic Paraplegia Foundation

How to Help

We operate out of the strength of our community, caring friends and sponsors. Your help makes a difference!

Please contact us at volunteer@sp-foundation.org to help in one of the areas below or to suggest another way you can get involved.

Support Research to Speed Our Cures by Volunteering

Below you'll find information on some of the ways you can help SP Foundation in their search for a cure to PLS and HSP.

Raise Funds: The primary focus of SPF is to raise funds to support research to find the causes, treatments and cures for Hereditary Spastic Paraplegia and Primary Lateral Sclerosis. Our major fundraising activity consists of a Team*W*alk. Individuals can help organize local fundraisers. People are also needed to secure corporate sponsorships and help with grant applications.

Patient Connection Programs: Organizing a Connections gathering for people to meet, share stories and help one another is a great service. Events can be as simple as meeting for coffee! In areas with large patient populations, SPF seeks to establish Chapters.

Conference Organizers: The SPF seeks event coordinators in or near metropolitan areas who can work with us to organize Conferences for our community. These events feature speakers and programs on special topics of interest to our community as well as provide the opportunities for individuals to meet others. Conferences can be half-day or full-day events.

Communications: Individuals with writing, research, website or graphic design skills are needed to assist with various communication initiatives.

Ambassadors: Ambassadors raise awareness about our disorders as well as enhance community building and industry relationships. You can assist with media relations, share your story, speak at local groups or help with grassroots advocacy.

Business and Administrative Support:
Volunteers with business and administrative skills can play a valuable role in administering the work of the SPF. Most of the help is coordinated through email correspondence and uses popular Office applications.

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The Spastic Paraplegia Foundation Inc. (SPF) is a national, not-for-profit, voluntary organization. It is the only organization in the Americas dedicated to Primary Lateral Sclerosis (PLS) and Hereditary Spastic Paraplegia (HSP).

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Letter from the President

Dear Friend,

I'd like to talk with you about your hope and happiness. I recently read an excellent and very informative book on genetics, "The Gene, An Intimate History" by Siddhartha Mukherjee. It covers everything from the first notion of genetics with Aristotle and Pythagoras to current and future genetic technology. The funny thing was that Aristotle should almost get the Nobel Prize. He virtually had it figured out over 2000 years ago.

One of the lines in the book that struck me, on about page 200, was that human beings and worms have about the same number of genes, around twenty thousand. The fact that only one of these two organisms is capable of painting the ceiling of the Sistine Chapel suggests that the number of genes we have is largely unimportant to the physiological complexity of the organism. The author wrote, "It is not what you have, it is what you do with it that matters."

It is with that analogy that I think people with HSP or PLS are given a gift. It is not what genes we have but what we do with them that matters. We have the choice of doing something with and about what we were given at the same time, (whether it be to volunteer or donate) - or not. Not everyone has such a clear choice.

Napoleon Bonaparte said "Courage is like love; it must have HOPE for nourishment." To that, I say that there has never been a time in history where there is more outstanding HOPE for a cure for HSP and PLS just on the horizon. Many of our research studies are getting to pay dirt. Believe it or not, we are preparing for Clinical Trials to begin with HSP as early as 2017 with two or three very hopeful new drugs. I wrote about this in our last Annual Report.

I collect quotes and I've got some good ones for you. Barbara Kingsolver said: "The very least you can do in your life is to figure out what you hope for. And the most you can do is live inside that hope. Not admire it from a distance but live right in it, under its roof."

I'm wondering if you might want to get under its roof with me? Why? Read this next one: Joseph Addison said there are, "three grand essentials to happiness in this life, something to do, something to love and something to hope for."

To do? We, of course, always need donations to speed up the timeline for a cure but we also need people to become part of our State Ambassador program. State Ambassadors are the people that welcome those that have just been diagnosed with HSP or PLS and need to talk to someone who is local. They feel like they are the only one on the planet with this disease and it is an overwhelming gift for them to have someone to talk to. The State Ambassador also hosts a social/informational gathering at a restaurant or church meeting room two or more times per year where people with HSP or PLS, along with their families, have the opportunity to meet others and ask questions. These gatherings are very rewarding for the host/hostess and the attendees. Attendees pay their own expenses.

If you would like to learn more about the possibility of helping or being a State Ambassador in your state, please call this number (877) 773-4483 to let us know. You'll be glad you did.

Sincerely,

Frank Davis
President

SPF Board of Directors

Board Business (April to August 2016)

Compiled by John Staehle

APRIL

- Mark Weber reported that requests for proposal were sent out to 139 researchers. The deadline for returning a research proposal for grant consideration by the SPF is June 13. Proposal guidelines have been posted on the website.

MAY

- Frank reported that the 2015 SPF Annual Report will be mailed on May 11.

JUNE *(at Chicago prior to Annual Conference)*

- The Board approved $400,000 to be used for research grants in 2016. The Board also approved an operating budget for 2016 including those grant monies.
- Mark Weber reported that we had received 16 research proposals for 2016 grants. All proposals were for HSP research projects. The Board discussed a number of alternate ways to incrementally fund PLS research programs that already exist.
- The Board approved a resolution to hold the 2017 Annual Conference in Atlanta, Georgia.
- There was much discussion on whole genome sequencing and the CRISPR technique for gene editing as they apply to HSP and PLS research. CRISPR is at a very early stage and its application to HSP and PLS are down the road. SPF grants are "seed" money that allows the researcher to gather more "ammunition", the data, needed when they approach NIH and others for significant research grants. Corey Braastad recommended we continue our approach of giving smaller grants to multiple researchers rather than "shooting for the moon" with a large grant to a single researcher.

AUGUST

- The Board re-elected its officers for another term: President, Frank Davis; Vice President, Linda Gentner; Secretary, Jean Chambers; Treasurer, David Lewis.
- The Board accepted with regret Kris Brocchini's resignation and praised her many years of service on the SPF Board.
- The Board unanimously elected three new members to the SPF Board: Laurie LeBlanc, David Ress, PhD and Ben Robinson.

New Board Members

Laurie LeBlanc

laurierleblanc@yahoo.com

Laurie is an Account Executive for an IBM Business Partner who specializes in IBM hardware and services. She completed her Bachelor's Degree in Management at Franklin Pierce University. Laurie was diagnosed with HSP in 2009 and became the NH Ambassador for The Spastic Paraplegia Foundation in 2010. She has helped with New England fundraising activities and has organized local gatherings. When not working, Laurie enjoys spending time with her family and her dogs. Her goal is to find a cure to prevent her children or grandchildren from having to suffer with HSP in the future.

David Ress, PhD

davidress@gmail.com

David Ress, PhD, is expert in many forms of scientific imaging including MRI, CT, electron tomography, x-ray imaging, and neutron imaging. He is presently an Associate Professor in the Neuroscience Department and Technical Director of the Center for Advanced MRI at Baylor College of Medicine. Dr. Ress also leads the High-resolution Brain Imaging Lab (HIRBIL), which focuses on developing new techniques to improve the spatial resolution and specificity of functional MRI, and applies these methods in the study of human neuroscience.

Ben Robinson

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Ben's career has focused on healthcare and higher education for close to 20 years. During these years he has worked for the numerous agencies of the state of Georgia, including the Georgia's mental health system, Medicaid agency and university system. In his current work for the University System of Georgia, he works closely with leaders of the Medical College of Georgia, 20+ state nursing programs and emerging leadership in the health informatics. He hopes to use these connections and knowledge of how healthcare systems work to further the research efforts of the SP-Foundation. In 1988 he received a bachelor's degree in history, with a concentration in Soviet Studies from Brandeis University and a master's degree in public administration from the University of Georgia in 1997. For fun, Ben plays out as often as he can, playing viola, guitar and bass.

CRISPR Update for Research and Therapy

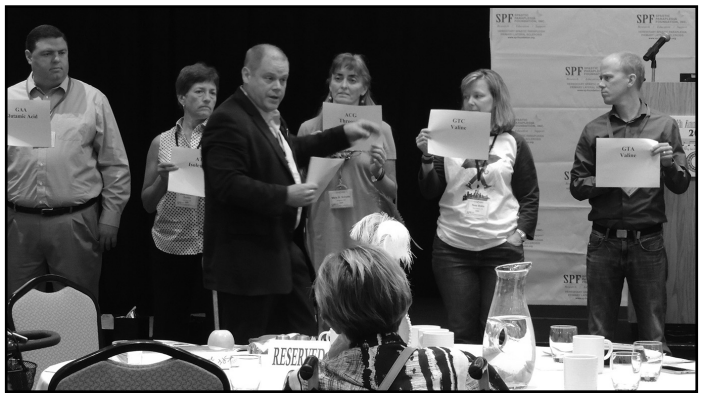
Corey Braastad, PhD, Vice President and General Manager Genomics, Covance Drug Discovery

Dr. Braastad introduced the attendees to CRISPR/Cas9 which is used as a research and therapy tool by editing specific DNA sequences. He explained how the process works by combining the CRISPR natural biological process, the Cas9 nuclease and our natural DNA repair processes to "edit" a targeted DNA sequence in a genome. Altering the DNA sequence of an organism for purposes of treating disease is called gene therapy. One important challenge of gene therapy is targeting the correct cells and editing enough cells to help with the disease.

Editing DNA sequences in cells is a very important capability for both research and therapy. For research, CRISPR/Cas9 can be used to create cells in a laboratory that contain DNA mutations that cause genetic diseases like HSP and PLS. The cells can then be studied to examine alterations in the biology of the cell and understand the cause of what is wrong in the cell. Once we know the cause of what is wrong in a diseased cell, we have a therapeutic target. For therapy, CRISPR/Cas9 may be used to edit the DNA sequence of diseased cells for a particular benefit to a patient. The first CRISPR/Cas9 clinical trial was given the "green light" by the National Institutes of Health (NIH) on June 21, 2016.

In order to better understand the meaning of editing the genome, Dr. Braastad revisited a presentation he had previously given on "Basic Genetics and Genomics of HSP and PLS." The purpose of this revisit was mainly to explain the biology of a cell and the biology of a gene. Within your body there are about a trillion cells. Almost all those cells have a nucleus (red blood cells are an exception) and within the nucleus are 23 pairs of chromosomes. If you stretch out the chromosomes you get the double helix structure of the DNA molecule. That is what CRISPR acts on, the DNA molecule. Within the DNA molecule are genes which contain the instructions for making proteins. Proteins can act alone or in complexes to perform many cellular functions.

Dr. Braastad then used audience participation to show how DNA sequences code for amino acids to make a specific protein. He demonstrated how a deleted nucleotide impacts one amino acid as well as subsequent amino acids including the position of the stop. The protein created by the change may be the cause of a disease.



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Dr. Braastad played an animated short produced by the McGovern Institute for Brain Research at MIT that is a graphical representation of the molecular CRISPR/Cas9 process. The short movie can be viewed at https://www.youtube.com/watch?v=2pp17E4E-O8.

Today CRISPR/Cas9 technology is available in just about any lab in the world and is heavily used on a routine basis for many research applications. The labs supported in part by SPF and other research in our field are actively using CRISPR/Cas9.

A major example of CRISPR/Cas9 in the news today is cancer immunotherapy. The first CRISPR/Cas9 human clinical trial was given a green light by the NIH Recombinant DNA Research Advisory Committee on June 21, 2016. The procedure targets bone marrow cells that are removed from the body, editing three immune response genes with three sets of CRISPR/Cas9 guide/nuclease/repairs, and introduced back into bones to establish changes in the immune system that attack particular cancers. This first trial is focused on safety and is funded by a $250 million immunotherapy foundation formed by former Facebook President, Sean Parker.

Risks of CRISPR include off-target modifications. We know that off-target modifications occur and those off-target changes are being measured and evaluated closely for safety concerns. So far, so good - despite early concerns.

CRISPR treatment of adults and children would NOT alter the germline cells (sperm and eggs), so the risk of passing along a genetic condition is not reduced.

CRISPR is personalized medicine to the extreme! The Duchenne Muscular Dystrophy CRISPR therapy is targeted to a single common mutation. SPG4 has a similarly common mutation, but most HSP families (and genetic forms of PLS) have distinct mutations in their families for which new CRISPR designs are required. Hopefully, FDA approval of these different CRISPR targets does not require an individual new drug application, which is an expensive and time consuming process.

To view the video of Dr. Braastad's presentation, go to http://sp-foundation.org/what_we_do/annual-conference-recap.html

Advances in HSP and PLS

John K. Fink, MD
Director, Neurogenetic Disorder Program, University of Michigan

Dr. John K. Fink, who also serves as the medical advisor to the Spastic Paraplegia Foundation, spoke to the conference on Saturday morning about the significant progress being made in research for both HSP and PLS. Compared to twenty-five years ago when SPG4 was first discovered, much more research is being done regarding these conditions. He indicated that now between 150 and 200 articles are being written each year about the research being done on HSP and PLS. In one weekend only two years ago, forty new gene mutations were discovered, yet he compared each new discovery to Columbus discovering a new country when he discovered America. "We have mountains of information, yet no cure and not many treatments yet," he continued.

In 2000, the medical community and researchers had only identified four mutations: SPG1, SPG2, SPG4 and SPG7. Now, there are more than 80 known gene mutations causing HSP, and some gene mutations contributing to some forms of PLS have been identified. One of those mutations, C90RF72, may also be related to ALS. He added that even though there may be no clear family history, there still could be a gene mutation involved.

Dr. Fink indicated that five years ago, researchers did not know the cause of PLS. Now, in some PLS cases, researchers have discovered it may be due to gene mutations. He called that "transforming" as it relates to PLS work. Upper motor neurons are vulnerable to a number of different issues and problems, he continued.

Dr. Fink then emphasized the need to get going on therapeutic challenges. He said it is important to develop treatment strategies that do not depend entirely on understanding how the gene works. He continued that there is an emerging concept that serial observation suggests that rates of functional worsening for many, but not all, subjects with PLS and HSP seem to slow. Reaching such a plateau may offer new approaches to the type and timing of various treatments to improve the lives of patients. Patients should be measured, particularly in terms of gait analysis on an annual basis. Serial functional

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assessment of many individuals with both HSP and PLS a number of years after symptom onset (e.g. 5 years) seem to show, in many times, relatively little change.

In conclusion, Dr. Fink strongly supports and encourages exercise for all HSP and PLS patients to the extent they are able to exercise. The exercises one does depend on the specific weaknesses and tightness the patient and situation present.

To view the video of Dr. Fink's presentation, go to http://sp-foundation.org/what_we_do/annual-conference-recap.html

During the afternoon breakout session, Dr. Fink made the following points in response to questions asked by conference participants.

- Ampyra: Insurance will not pay for the use of Ampyra by HSP patients. He indicated that it has helped only 10-20% of the HSP users he knows that have used it. Many saw no benefit at all. He thinks new symptomatic drugs will be developed possibly every year.
- SPG4, SPG3A and SPG7 are the most common HSP gene mutations. Many gene mutations have only been found in two to three families.
- Vitamin E: A little is good, a lot can be toxic. He suggested no more than 400 units daily for an adult.
- CoQ10: While its benefit has not been scientifically proven, Dr. Fink has prescribed it, generally less than 400 mg/day, to both HSP and PLS patients to slow down the oxidative process.
    - Generally, we want to find treatments for many different gene mutations. Treatments probably will not come for specific mutations.
    - Botox can be very effective for spasticity, but not if ankles, knees, and abductor muscles are all very tight. Tightness in just one place is a much better area to use Botox. Do everything possible before considering a dorsal rhizotomy, tendon lengthening.
    - Strength is more important than flexibility for walking. One cannot walk without strength.
    - In regard to gene therapy, both HSP and PLS involve degeneration. We do not know whether gene therapy can regenerate the broken nerve cells. The goal is to reverse the symptoms.
    - Dr. Fink is not aware of any studies that a change in diet affects spasticity.
    - For those considering the baclofen pump, the trial is very important. The most important question is whether or not walking is improved and not does it reduce the spasticity. If pain is your problem, then you need to determine the cause of the pain to determine the proper treatment. If a person has a lot of weakness to start with, a pump probably is not a good idea.

Summaries of Dr. Fink's presentation and break-out Q&A session were prepared by Greg Pruitt.

Potato Pants

Lori Renna Linton
High School Teacher with HSP, Kritzendorf, Austria

This year at the SPF Annual Conference we had the benefit of hearing from the creator of the latest fundraising event to come to us from "across the pond." **Lori Renna Linton** came from Austria and explained to us the creation process that prompted her need to let others "feel" what it's like to have a mobility disability like Hereditary Spastic Paraplegia.

According to her YouTube video, the need arose after hiking with her daughter and friend. (www.youtube.com/potatopants)

Lori has even made a "How To" video on "How To Make Potato Pants", so that you can make a pair for yourself and to share your daily experience with others. (www.youtube.com/potatopants/how to make pants)

Included in her presentation was a live demonstration with Scott and Maritza Meurer, of Colorado, who volunteered to "wear" the potato pants and do ordinary tasks like walking up a ramp and stairs. "Just trying to balance as I walk is hard! The weight [of the potatoes] keeps shifting," said Maritza. "It was really eye-opening for me. So this is what my daughter feels like everyday!" realized Scott.

The main takeaway here is enlightening others with what it is like to have HSP.

Summary prepared by Tina Croghan.

Multi-Modal Neuro-Imaging in People with PLS

Sabrina Paganoni, MD,PhD

Assistant Professor of PM&R, Harvard Medical School; Massachusetts General Hospital, Neurological Clinical Research Institute

Dr. Sabrina Paganoni spoke about her PLS research. Specifically, that she has been doing multi-modal neuro-imaging research which is a more sophisticated version of the brain MRI tests that many people have had. Upper motor neurons are located in the part of the brain called the upper motor area, the part of the brain that controls movement. The cell bodies of the upper motor neurons project axons which form the cortical spinal tract. This is the tract that connects the brain to the spinal cord and that is where the problem is with PLS.

She reminded everyone that she is the second recipient of the Virginia Freer-Sweeney Fellowship, an SPF collaboration with NEALS (the North East ALS consortium of universities). The first recipient of this fellowship was Christina Fournier, MD, from Emory University. She published her study which mapped out where people with upper motor neuron diseases live and where they are being seen.

Last October, Dr. Paganoni started her two-year study of PLS. In addition to her Fellowship goals of improving our knowledge of PLS and leveraging new knowledge to find treatments for PLS, an important goal is to establish a community of scientists who are dedicated to the study of PLS. An outcome of the Fellowship is that NEALS has established an Upper Motor Neuron Task Force, an interest group of scientists who are focusing on the study of upper motor neurons.

The goal of NEALS is to study ALS but it also works on upper motor neurons as a subtype. There are 1000 to 1500 people with PLS in the US. There are 25 academic centers where people with PLS are seen. NEALS had been studying about 50 people with PLS but are expanding the study to about 300 people with PLS over 25 sites and 5 other countries, Canada, Mexico, UK, Australia and Israel.

Dr. Paganoni started the review of existing data on the natural history of PLS in January and is in the middle of the process. She plans to have results by December and expects to report progress and results at SPF's next Annual Conference in Atlanta. One of the main benefits of this study is to find out what is normal for PLS progression. When treatments begin, doctors will have a measurement to see what sort of improvements are actually taking place compared to what would have been expected without those treatments.

Dr. Paganoni acknowledged she has some very good mentors in the PLS study field. Mary Kay Floeter MD PhD, works for NIH and NEALS and currently sees about 80 patients with PLS. She has been making various clinical measures of those patients over the last 15 years. These measures include gait speed, finger tapping, foot tapping and hand dexterity. She also has gathered some imaging data.

Dr. Paganoni's other mentor is Hiroshi Mitsumoto MD from Columbia University. He is an international leader in upper motor neuron studies. He has a Cosmos Study where he is looking at biomarkers, mostly for ALS, but he does have a sizable number of people with PLS involved. He is currently applying to NIH for funding for a study that they call "Clinical Trial Readiness". NIH is now supporting projects that will improve the chances of success of a clinical trial. They want to establish specific outcome measures for PLS. There will be about 20 NEALS sights that will be doing the data collection.

She is also working with Nazem Atassi, MD, Massachusetts General Hospital. Dr. Atassi has a PLS program at MGH and is the Director of the Virginia Freer-Sweeney Fellowship.

Dr. Paganoni said that not much of the definition of PLS has changed since it was established in 1992 in the original Pringle paper. The criteria was slightly changed in 2006 with the modified Gordon criteria but the original 1992 description of PLS is largely still used. PLS is a clinical diagnosis which means that there is not one single test to determine whether a patient has PLS. Basically, the doctor has to rule out everything else. A goal is to come up with a test that can be used for diagnostic purposes. Additionally, the way the criteria is currently set up, a patient has to wait 3 to 4 years before the diagnosis is really definitive.

PLS affects the motor cortex in the brain or the part of the brain that controls motor function or movement. The cells in this area of the brain are called upper motor neurons

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and they project axons into the cortical spinal tract. The cells in this area are called pyramidal Betz cells from the name of the person that described them. They know from a few autopsies done in 1996 by Dr. Pringle that people with PLS lose these upper motor neurons. They are replaced by glial cells which are normally supportive cells in the brain. Something happens in patients with PLS and ALS where the microglia and astrocytes become reactive and become activated such that the axons die off with time.

They have been doing multi-modal neuro-imaging using three different types of measurements. The first is Structural T1-weighted imaging where they take a picture and measure the cortical thickness in motor cortex. Another measurement is Diffusion Tensor Imaging (DTI) where they measure the fractional anisotropy as a proxy for changes in tissue microstructure. The third measurement is Positron Emission Tomography (PET). PET can be used for diagnostic purposes. PET is used to study not structure but function and it depends on what they inject into the brain as to what is measured. At MGH they use a combined PET system. They can overlay results to look at both structure and function at the same time. They are using a PBR28 radiotracer. The reason they are using this one is because it binds to the glial cells which become reactive or active and transform themselves from being supportive cells to being toxic cells in people with PLS. This tracer is a nuclear medicine tracer with a very short half life. They have onsite a nuclear medicine machine called ayclotron which produces the PBR28 which has to be manufactured a few days before it is used. Timing is critical as it is only good for a few hours.

In this study they scanned the brains of 21 people which included 7 with PLS, 7 with ALS and 7 were healthy controls. They are planning to increase the population in the future. Their measurements showed that people with PLS have marked increase in microglia & reactive astrocytes. This activity is located in the anterior part of the brain which is the area affected by people with PLS. It is increased in people with ALS as well but not as much. People with ALS have upper motor neuron problems but not as much as people with PLS. They have found that the more the inflammation of these cells that surround the motor neurons, the thinner the motor neurons become. They also used the DTI technique to measure reduced fractional anisotropy in the motor cortex. This means that the microstructure of the cell is altered so there are some problems with the axons that form the corticospinal tract.

In conclusion she said that this type of measurement provides a biomarker to measure the progression of PLS. There is more uptake in the regions of interest which are the Primary motor cortex and the corticospinal tracts which are the areas affected in the brains of people with PLS. This progression correlates with clinical features of people with PLS, such as spasticity and difficulty walking. They can also measure cortical thinning and fractional anisotropy in people with PLS. This is a proxy for neuronal loss and disruption of tissue microstructure.

The next step is to increase the population by examining more patients with PLS to confirm their results. This is a very expensive process as each scan costs about $5,000. They also want to follow people longitudinally, i.e., over time. They want to see if their measurements continue to correlate with how people feel. They plan to correlate their measurements with Dr. Floeter's data to see how her clinical measurements correlate with the imaging results. Dr. Paganoni also wants to recruit people with PLS earlier, preferably right on symptom onset. She hopes to use this as a diagnostic tool to be better able to distinguish PLS from ALS at the very beginning and avoid the 3 to 5 year waiting period to definitively diagnose a patient with PLS. She also wants to be able to use this measurement tool as a measurement for how a Clinical Trial is working with patients with PLS. They will be able to see if a drug is affecting the very areas of the brain that are the problem with people with PLS.

Dr. Paganoni said that it takes a team to accomplish these results. First of all, it takes funding and the Spastic Paraplegia Foundation has funded her research for two years as well as a portion of the scanning that the team has been doing. It also takes the participation of patients who are willing to partake in these measurements with MGH's scanner. She also thanked Merit Cudkowicz, MD who is the co-founder and co-director and former chair of NEALS and Nazem Atassi, MD who runs the MGH Lab for imaging in Motor Neuron Disease in the MGH PLS Program.

Summary prepared from extensive notes taken by Frank Davis. To view the video of Dr. Paganoni's presentation, go to http://sp-foundation.org/what_we_do/annual-conference-recap.html

PLS: The Way Forward

Teepu Siddique, MD, PhD; Les Turner ALS Foundation/ Herbert C. Wenske Foundation Professor; Professor, Department of Neurology and Cell & Molecular Biology, Director, Division of Neuromuscular Medicine, Northwestern University, Feinberg School of Medicine

Dr. Siddique began by defining Primary Lateral Sclerosis: Primary means the main reason, no other illness is involved; Lateral means it affects the fibers that run from the cortex of the brain to the sides of the spinal cord; and Sclerosis means those fibers have been replaced by harder fibrous tissue, as in a healed wound.

A PLS diagnosis is one of exclusion. Doctors perform tests for the motor neuron diseases that have them and if they all come back negative, then you might have PLS. Unless you present other symptoms of PLS, you may have to wait several years for a definitive diagnosis.

PLS was first described by Charcot. It was widely accepted as Charcot was often thought of as the "father of neurology." A pupil of his, named Marie, proposed that PLS was not a single disease but manifestations of several other diseases. In the latter half of the last century, a Canadian neurologist named Pringle was the first to establish the criteria of PLS.

Signs and symptoms of Upper Motor Neuron (UMN) degeneration are increased muscle tone and spasticity, hyperactive reflexes, clonus, decreased ability to do fine movements such as finger tapping and a positive Babinski (up going toes).

In 2001, the Northwestern University Feinberg School of Medicine (NUFSM) became interested in PLS research when they found a mutation of the ALSIN gene as being responsible for a recessive form of ALS and juvenile PLS in families. They discovered mutations for ALS and PLS on different sites of the gene. The PLS mutation occurs in exom9 present in the longer form of the gene and the ALS mutation occurs in exom3 present in both the long and short form of the ALSIN gene. This discovery led to a hypothesis that identified the first "cause" of PLS.

The publication of this finding piqued the interest of adult onset PLS patients. It became apparent there was a need to collect samples from that group. However, since PLS was such a rare disease, there was a limited and yet unknown patient population with no network in place to help identify them. Collecting samples would be a very long term project. A decision was made to use a registry format to maintain data and materials for future research.

Four women with PLS, Thurza Campbell, Angela Dixon, Linda Gentner and Jennifer Thomson, and the Spastic Paraplegia Foundation (SPF) pushed for serious research into PLS. In 2004, the Chaminade Conference on PLS, the first of its kind and partially funded by the SPF, was held in Santa Cruz, CA. At this 3-day conference the attendees reached a consensus on proposed diagnostic criteria to promote consistency from center to center and to meaningfully separate PLS from similar conditions. The Chaminade Criteria to diagnose PLS are

- **Suspected PLS**: Signs of UMN degeneration in 1-2 regions, no obvious explanation for these; and no LMN signs (marked atrophy, fasciculations and EMG changes).
- **Probable PLS**: UMN signs in 2 regions for 3 or more years; and still no EMG signs.
- **Definite PLS**: UMN signs in 3 or more regions for 5+ years; no LMN signs; and UMN predominant ALS after many years.

The criteria to differentiate PLS from SP and ALS are

- **SP**: UMN signs in lower extremities; possibly increased reflexes in upper extremities; and other conditions such as hearing and vision loss and ataxia.
- **ALS**: UMN and LMN signs and EMG evidence.
- **PLS**: UMN signs in multiple regions over a long period of time.

The NUFSM PLS Registry started with the chart review of 379 possible patients. After the first chart review, the total number of possible patients was reduced to 293. A second chart review ten years later left 191 totally vetted PLS patients in the Registry. There was enough information to make a case for genetics and proceed with Whole Exome Sequencing (WES).

WES examines the DNA sequence of the genes that code for proteins. Exomes are thought of as the "working part" of your genetic material. Exomes make up only about 1% of the whole genome but are thought to contain about 85% of the disease causing mutations. Consequently, it is relatively cost effective compared to whole genome sequencing. Even so, it creates a massive amount of data which presents challenges in organizing and prioritizing parameters for analysis. Dr. Siddique described some of the methods being used to process the data all of which have the possibility of missing data such as DNA repeats, deletions and intronic mutations.

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Dr. Siddique concluded his presentation with an update of where they are with PLS and WES project. They are completing very careful chart reviews to make sure the appropriate samples are screened. During the next 4-6 weeks, they will be screening 100 additional patients, funded by a grant from the SPF, followed by the time-consuming detailed data analysis. "Hits" that are identified by that analysis will be checked by sequencing the genes containing the "hits."

To view the video of Dr. Siddique's presentation, go to http://sp-foundation.org/what_we_do/annual-conference-recap.html.

How Do People Move: Measuring Function in Pediatric Patients with HSP

Dr. Tulchin-Francis PhD, Director of the Movement Science Laboratory, Texas Scottish Rite Hospital for Children, Dallas, Texas

Dr. Tulchin-Francis began by saying that she would be speaking much more about the effects of HSP rather than its causes. She has been working at Texas Scottish Rite Hospital for Children (Scottish Rite) in Dallas for the last 15 years. Scottish Rite conducts a special monthly clinic devoted to children with HSP. This Pediatric HSP Clinic is managed by Dr. Mauricio Delgado MD, PhD and coordinated by Linsley Smith RN BSN. In addition to the clinic, Scottish Rite also has research projects to improve the diagnosis and care of children with HSP. These research programs encompass the development of a clinical database, imaging, genetic research and functional measurements of gait and activity levels.

Dr. Tulchin-Francis is the director of the Movement Science Lab. The lab's process starts with a clinical exam of the patient. They then do a very careful video assessment using 12 cameras to measure reflections from markers attached to the patient's body. The measurements go into a computer where they are recreated in 3 dimensional space. They also They measure strength in two ways: first they just feel how strong the patient is and then follow up by doing quantitative strength measurements with dynamometers. They use computerized gait analysis and plantar pressure analysis, using plates on the floor to measure the force against them as the patient walks and where on their feet the patient is walking. The Lab measures oxygen consumption - the more a patient uses their muscles, the more oxygen they need. It is not only the quantity of oxygen used but how efficiently the patient uses the oxygen to function. Heart rate is another easy measurement they use to see how difficult it is for the patient to move. Lastly is what she calls community measures, things like how does the patient function in the community when they go to the grocery store and the number of steps they take in a day. These measurements are mainly made using wearable sensors.

The Lab uses all of these measures to calculate how much power is being exerted by the patient's different muscles while performing various body movements. This is called kinematics or the forces that power movement. They also can put instruments on walkers and on parts of a wheelchair to measure how much force is being exerted when a patient is using them. They use these measurements to help the doctors decide which treatments to use. The doctors can then determine whether or not the patient should have therapy or whether or not a specific kind of leg brace or AFO would be appropriate. The data can also be used to recommend to the doctor which particular kind of surgery or medicine to recommend. They also use these measurements for various research projects. Dr. Tulchin-Francis said that about 80% to 85'% of Scottish Rite Hospital is used for research and about 15% for clinical. One of their strongest research departments is with the HSP population.

Dr. Tulchin-Francis then spoke at length about all of the different phases of a person's walk, beginning with their weight balanced on two legs. They then go into a swing phase where the weight is supported by one leg and a lot of muscles interact to maintain balance. As the person descends, there is a time when the other leg goes through what she called "weight acceptance" and weight is transferred off of the other foot. There is another phase, called propulsion, where the person has to get their leg to move forward with their hip flexors which pull their leg off the ground and ankle plantar flexors and calf muscles that push their leg off of the ground.

Rather than looking at stick figure animations of this process, the doctors at Scottish Rite prefer to look at four graphs that describe how the pelvis, hip, knee and ankle move when somebody walks. Each of the graphs begins when the foot leaves the ground and end when the foot hits the ground again. A specific patient's graphs are compared to the "control" graphs of a normal gait. They use these measurements to quantify just exactly how a patient is walking and then be better able to measure how a patient's walking has or has not improved after surgery or after being treated with certain medicines. It also can be used to measure the progression of progressive diseases such as HSP.

Continued on next page

In the United States, there are a lot of misdiagnoses of HSP as Cerebral Palsy. There is much research about CP in children, but there is very limited research about HSP in children. The quest to distinguish HSP from CP using gait analysis has not been very successful to date. The movement Science Lab uses a multifaceted and multidisciplinary effort. They work closely with Scottish Rite's physical therapy and neurology departments. They look at clinical exams, the data your doctors are collecting already, including active or passive motion, tone and spasticity assessment and gross motor function. The Lab follows this with an instrumented gait analysis. They also perform the 6 minute walk test which asks the patient to see how far they can walk in 6 minutes. They also measure oxygen consumption while they are doing the 6 minute walk test to find out how much energy they are expending in performing the effort.

Dr Tulchin-Francis then showed us an example of one 12 year old girl's walk and her Lab measurements. She then compared this to a film 3 years later and then another one still 3 years later where the patient was using a walking aid. She showed how the measurements allowed the doctors to better find out how the patient had gotten worse.

The second example was a video of a boy with HSP and his gait difficulties. He had undergone multiple gait surgeries and had a baclofen pump implanted, but did not show much improvement after the surgeries. His twin sister has had no surgeries, does not have a baclofen pump and has had no Botox injections. She has a very different clinical presentation even though they have the same genetic variant of HSP. With the analysis of their measurements, the Movement Science Lab personnel can quantify the differences.

Dr Tulchin-Francis presented a study of 27 different patients ranging in age from 7 to 35 years with an average age of 14. Each walked for a gait analysis and performed the 6-minute walk test. Measurements were taken for distance walked, oxygen consumption and heart rate during the 6-minute test. The Lab developed a gait score using a combination of gait-related measurements which they named the Gait Deviation Index or GDI. A normal gait has a GDI of 100 and every 10 degrees away from that is a standard deviation away from normal. A GDI of 90 means a person is a pretty good walker; 80 is a little worse; and at 20 or 30, a person is really struggling to walk. The worse the walking is, the higher the oxygen usage. The Lab uses the Fitbit fitness tracker to collect some of the data. They also use 3D accelerometers which use the same technology as the fit bit but are more accurate and also allow the researcher access to the raw data. They are still collecting and analyzing data.

Dr. Tulchin-Francis then presented the Texas Scottish Rite Hospital Treatment Paradigm. Their Goals are:

1. Task Specific Training, Strengthening
2. Orthosis, Adaptive Equipment, Mobility Aids
3. Ortho Surgery
4. Casting
5. Tone Management

Dr. Tulchin-Francis thanked the Spastic Paraplegia Foundation for inviting her to speak and took questions from the audience.

Summary prepared from extensive notes taken by Frank Davis. To view the video of Dr. Tulchin-Francis' presentation, go to http://sp-foundation.org/what_we_do/annual-conference-recap.html.

2016 Annual Conference and Plans for 2017

Tina Croghan, 2016 Conference Coordinator

I think it's safe to say that the Annual Conference in Chicago this year was a great success and enjoyed by all! There were 147 registered attendees for Saturday's sessions and 53 registered for Sunday's "field trip" to the Abilities Expo in a nearby Chicago suburb. The Conference's success is really evident in your responses taken from the survey of those attending. Before I share the information that we garnered from the survey, I want to take this opportunity to thank those of you who participated in it. Because of your responses, we were able to "tweak" a few items on the agenda.

The survey was sent to 62 people with 39 responding. While the tentative agenda for Atlanta reflects some differences, the overwhelming majority of you felt that the conference length was about right. The intention now is to maintain the same time, but alter the length of each presentation allowing for a restroom break between each speaker.

Two-thirds of the responders said they would attend more breakout sessions as long as they don't conflict with Dr. Fink's session. We are going to try this out next year and offer more breakout sessions, none of which will conflict with Dr. Fink's Q&A session.

The conference in Atlanta is tentatively scheduled for the same time next year, June 22-24, the weekend after Father's Day and the weekend before Independence Day (USA). Of course this is all dependent on the availability of the hotel, which has not yet been chosen. We still need to make a site visit of the hotel and find out how accessible it really is. I'm sure all of you are aware that "accessibility" is a relative term!

If you would like the entire results of the survey, please send an email request to tinacroghan@yahoo.com..

DISABILITY LAW: Copyright, An Overview

By Mary B. Schultz

One of the benefits of membership in SPF (Spastic Paraplegia Foundation) is the sharing and support of others who have HSP (Hereditary Spastic Paraplegia) or PLS (Primary Lateral Sclerosis). That sharing and support is defined by the application of copyright law. For that reason, I intend to devote several columns to application of copyright law in the United States to the distribution of reports and articles about research relating to HSP or PLS. In this column, I hope to provide a few fundamentals of copyright law.

The Copyright Act of 1976, 17 U.S.C. §102 *et seq*., is the codification of copyright law in the United States. The 1976 Copyright Act was to promote the progress of science and useful arts, and conform to the standards of the Universal Copyright Convention (UCC). Section 102(a) of the 1976 Copyright Act spells out basic copyright protection. 17 U.S.C. §102(a). The 1976 Copyright Act confers on the owner of a copyright the exclusive right to do certain things, including making copies of copyrighted material and distributing copies of copyrighted material to the public. The 1976 Copyright Act did not go into effect until the beginning of the year in 1978, and has since been amended several times. In addition to codifying copyright protection, the 1976 Copyright Act provides for certain limitations on copyright, most notably the "fair use" doctrine (17 U.S.C. §107). (The "Fair Use" Doctrine will be addressed in a later column.) Significantly, copyright protects *expression* of ideas, not *ideas* themselves. In addition, *facts* and *statutes* cannot be copyrighted.

Copyright is automatically granted to an author of an original work. Registration is not required. However, registration is required before a lawsuit may be filed for infringement, and registration allows for certain statutory damages that are otherwise unavailable. Injunctive relief, a court order providing for prevention or restraint of copyright infringement, is also an available remedy. Injunctive relief and recovery of monetary relief may be sought simultaneously. They are not mutually exclusive. The doctrine of "innocent infringement" is a defense to a claim of copyright infringement. (The "innocent infringement" defense will be addressed in more detail in a later column. Generally, "innocent infringement" is made without knowledge or awareness that an act constitutes copyright infringement. Generally, application of the "innocent infringement" defense limits relief to injunctive relief, and exempts liability for monetary damages.)

A 1996 amendment to the 1976 Copyright Act, is known as the "Chaffee Amendment". 17 U.S.C. §121. The Chaffee Amendment permits a not-for-profit organization or a government agency to reproduce copyrighted works in a specialized format (like braille and audio or digital text) for use by the blind or persons with certain disabilities.

The United States Copyright Office handles copyright registration, and has other administrative functions of copyright law.

The effectiveness of copyright law to promote the progress of science and useful arts is often disputed.

Mary Schultz is a partner is the law firm of Schultz &Associates LLP, www.sl-lawyers.com , 640 Cepi Drive, Suite A; Chesterfield (St. Louis), Missouri 63005, (636) 537-4645. Mary B. Schultz graduated from Northwestern University Law School more than 30 years ago, in 1985, and has been practicing primarily in Missouri ever since. Mary B. Schultz is admitted to practice in Missouri and Illinois.

Mary Schultz was diagnosed with HSP in 2012, and through genetic testing has learned that her gene mutation is in SPG7. Mary has been a member of SPF, and has benefited from friendships and support she has received through SPF.

This column is intended to provide general information only. It does not constitute, nor should be relied upon, as legal advice or a legal opinion relating to specific facts or circumstances.

North Texas SPF Connection
May 14, 2016

By John Staehle, SPF State Ambassador, North Texas

John Staehle, North Texas SPF Ambassador, hosted the Spring North Texas SPF Connection on Saturday, May 14th in the Gathering Room at Advent Lutheran Church in Arlington, Texas. Our group for this Connection numbered twelve. The format for this informal gathering was the same as the November Connection and each attendee brought a snack to share. After introductions, John updated the group on the number of SPF contacts in the North Texas region, a total of 83, of which 62 have either a diagnosis of HSP or PLS or are a spouse/caregiver/family member of someone diagnosed with HSP or PLS. Nineteen of the 62 have PLS and 15 of them live in or very near the Dallas-Fort Worth area.

Subjects discussed included the 2015 SPF Annual Report that was mailed to SPF members and donors; the 2016 SPF Annual Conference held in Chicago, June 24-26, 2016; post-implantation issues with baclofen pumps; the Pediatric HSP Family Conference hosted by Texas Scottish Rite Hospital for children (attended by connection attendees Sara, Dorothy, Noah and Avery Taylor, Carol Hawthorne and Frank Davis); the Consortium of Spastic Paraplegia Support Groups, an international organization with representatives from Australia, Euro-HSP (the Federation of European HSP Associations), the United Kingdom, the United States (represented by Frank Davis), Denmark, France, Italy, The Netherlands and Norway; the variety of medications we take, their effectiveness and side effects; and personal experiences dealing with HSP.

The Fall North Texas connection is planned for November 2016. For more information, email John Staehle, jstaehle@swbell.net.

Standing L to R: Mike Rudd, Carol Hawthorne, Laura Ford, Dorothy Taylor, Noah Taylor, Avery Taylor, Sara Taylor, Reagan "Nikki" Holmes, Jerry Holmes.
Seated L to R: Sue Rudd, John Staehle, Frank Davis.

SPFIllinois Connection
August 13, 2016

By Sid Clark, HSP and Hank Chiuppi, PLS

It is good when you have a Connection and everyone has fun and wants more. On Saturday, August 13th SPIllinois had its 12th Connection or get together. Yes, we have an agenda but it is more of a round-robin of the 18 there to share, ask, and contribute to our common good. We covered among other subjects: a review of SPF 2016 Annual Conference, Dr. Corey Braastad's great presentation [Gene>DNA>(4) bases (A&T,C&G), (3) Bases > Amino Acid> Proteins] and the promise of CRISPR, 2 members contributed handouts of their exercise programs (do regularly), 2 contributed a discussion on Cannabis (requirements for a card, cost, and just how effective it is), Charcot-Marie-Tooth disease (CMT) vs HSP/PLS (peripheral vs central nerves), Scooters vs Power Chairs, ADA Handicap facilities or lack of it when traveling, sticking up for your rights, stair lifts, recommended Physical Therapists (refer to American Physical Therapy Association, ask if they have neuro therapist), and some fund raising activities, e.g. Linda's virtual walk and an informational HSP/PLS booth at a local fair (raffle of a basket of goodies contributed by us).

We ordered box lunches from Corner Bakery and had the driver take the Connection picture. We cannot wait for another get together. Our next Connection will be mid October. For information on future meetings, email us at SPFIllinois@gmail.com.

Attendees L to R: Mike, Ed, & Anne Sopala; Candy & Andy Cotsiomitis; Lynn Staudacher; Joan & Ashley Morris; Paulette Chiuppi; Carolyn & Sara Wright; Sid & Carol Clark; Phyilis & Frank Madrigali; Hank Chiuppi; Regina Potts; and Sue Tipton.

Austin Patient Connection
August 20, 2016

By Marlene Doolen
SPF State Ambassador, Central and South Texas

The 2016 Austin Texas Patient Connection was held August 20, 2016 with 20 people attending. It was a wonderful time for people to meet with others who have Hereditary Spastic Paraplegia (HSP) or Primary Lateral Sclerosis (PLS). We visited and shared information with each other. As the SPF State Ambassador for Central and South Texas, I host a Patient Connection each year in Austin. I know what it felt like to be the ONLY one you know who has a rare disorder. Meeting others with the same rare disorder helps in getting information and can change lives in how they are lived. Three years ago at an Austin Patient Connection, one of the attendees showed me a scooter she had, which I went and purchased online. This device changed my life by increasing my independence to do more and get things done faster. The photo shows those that attended this year's connection.

For more information, contact me at MDoolen512@aol.com.

The Good Old Days

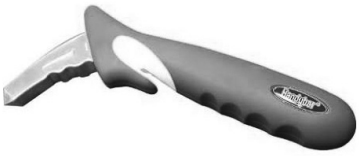
The good old days weren't as great as we remember, but the present isn't as bad as you think – and the future will be better than you expect.

~ Morgan Housel

Tina's Tips...

From Frank Chiuppi, Illinois State Co-Ambassador

Door Grab Bar



There have been a number of good hints presented in Tina's Tips. This one I said "no" to 2 or 3 times: a DoorBar, DoorCane, and car grab bar. When I had the scooter lift installed in our car they wanted to sell me one – I said no. But recently the medical supply house did some work for me and threw one in as a freebee. I use it every day now! This auto assist grab bar slides into the auto door striker or latch and allows me to stand and pivot to get on my seat in the car. It gives support when standing entering or exiting the car. I can not stand unsupported and this grab bar does exactly that, support my standing and prevents me from a fall. Even if you are just unsure of walking or standing this will help give you peace of mind. It required no adjustment to my van and pulls out for storage in a side pocket when we are driving. It helps continuing independence and improves mobility. There are many different brands with varying features.

Use GoodSearch and search for "door grab bar". You'll find there are multiple products and sources for these low-cost aids. Don't forget to use GoodShop when you buy your door grab bar and SPF will receive a percentage of the purchase price. [Ed.]

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