

Synapse

Volume 15, Issue 4

Fall, 2012

Newsletter of the Spastic Paraplegia Foundation

Letter from the President



Dear Friends,

During the last several months my wife, Claudia, and I have moved to a new home about 45 minutes away from Dallas. During that time, our long-haired miniature dachshund, Maddy, kept looking at us with questions on her face about whether we realized that things like furniture and pillows were disappearing from

her environment. Didn't we know that so many things that made her life special were gone?

Then, on the day when we finally made the move, she recognized all of her familiar and comfortable things in our new home. Even though it was a bit messy and awkward for several weeks, it was comforting and reassuring for her to become reacquainted with things that had slowly been taken away from her. Now her life was truly good again.

I like to think that this is how things will be as we move closer to a cure for HSP and PLS. Think about how great it will be as we recover what has slowly been removed from our lives and we become reacquainted with our familiar ability to move and walk?

As I have said before, real medical discoveries and improvements in our lives are within reach but it is up to

us to do the reaching. Please do not let the end of the year arrive before making your financial pledge toward that happy new home of a cure.

Your Spastic Paraplegia Foundation Board of Directors are extremely busy. Our new web site has just been rolled out. Much information and many photos have been added. We plan to regularly update the new site with news and information you can use so please visit sp-foundation.org often.

We've also been working with Combined Federal Campaign groups, several different neurological conventions, the National Organization of Rare Diseases (NORD) and Abilities Expos around the country to spread the word about the SPF. Dr. Malin Dollinger and our new newsletter editor and board member Allen Bernard are writing an informative medical booklet about HSP that we plan to distribute to neurologists around the country.

We have been working with our scientific advisory board on new exciting research proposals. Every year, knowledge builds upon previous knowledge as we climb that scientific ladder toward the day when cures can be announced.

You should be receiving a letter from me in the next couple of weeks where we will celebrate together all that our Foundation has accomplished. I'll share how we look forward to a very productive 2013.

Frank Davis
President, SPF

MARK YOUR CALENDARS!

The next SPF Annual Conference is scheduled for June 14 & 15, 2013 at the Renaissance St. Louis Airport Hotel in St. Louis, MO. For those that attended in 2009, it's the same hotel!

Registration opens January 7, 2013 so book early and we'll see you there.



Editor's Note

Hello, my name is Allen Bernard and I am the new *Synapse* editor as well as a member of the SPF board of directors. I am taking over from some very capable folks namely Beth Anne Shultz and fellow board member Annette Lockwood and would like to offer up a big "Thank You" to both of them for their hard work on the newsletter and dedication to SPF.

We've got a lot in this issue about research and then a couple of notes about rock climbing and equine therapy from members, which are just as important. More so in many ways. My wife and I have been around horses for years and they are very therapeutic. If you get a chance, try some horseback riding to help with your HSP or PLS. You will feel better after you're done.

Another member sent in a note about her first indoor rock climbing experience. For folks with less advanced HSP this can be a good way to help stay in shape and have more fun than just doing PT all the time. I used to climb in my younger days and it too is very therapeutic, calming and a great workout.

Swimming too has helped our daughter. It was in a large hot tub that she first began to walk in the summer of 2011. With her body supported by the water she was able to get a feel for how her legs were supposed to move. It took a while but a year ago October she was finally able to translate that movement in water into movement on land and she's been getting better and stronger ever since. She still has HSP but she can actually run now.

So get out and move as much as you can. As former board member Dr. Malin Dollinger points out in his article about the Esko Exoskeleton, keep yourselves as physically strong as you can for as long as you can so when researchers do find a cure, you'll be able to take advantage of it.

Take Care,

Allen



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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).

Synapse Editor

Allen Bernard.....Senior Editor

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Events and Teamwalks

Philly Team Walk

On Saturday September 8, 40 people met in the parking lot of Magee Rehabilitation Hospital to raise funds for research and share their experiences. People met at 10:30 AM with a lot of smiles. Then the group then proceeded on a walk through Philadelphia. After an exhausting walk the group had a wonderful lunch provided by Magee Hospital. At lunch Dr. David Lynch, a prestigious neurologist from University of Pennsylvania spoke on recent developments in HSP/PLS research. The TeamWalk produced a lot of new friendships and raised about \$1,100 dollars for research.



CATW Raises over \$70,000

by Linda Gentner

The 10th CA TeamWalk For Our Cures (CATW) weekend was held on September 21 and 22 in Pleasanton and was a resounding success. We dedicated this weekend to our dear friend Ken Auer who passed away on Memorial Day of this year.

Ken, and his wife, Julie have always been significant participants to make our CATW a success. Our Friday night welcome dinner had 28 people in attendance. After enjoying a lovely dinner, we adjourned to a private meeting room for dessert and our Up Close and Personal discussion time. Linda arranged for a cake decorated with the TeamWalk logo and chocolate dipped strawberries as well as a white chocolate favor at each place setting to celebrate our 10th CATW.

They were in a cellophane bag with a green ribbon with 10th anniversary imprinted in gold. It was a nice special touch. With that many people in attendance, it took quite a while for everyone to share — patients and caregivers were given equal time to say what they wanted to say and ask questions. No one felt that they were alone with their disorder after leaving the meeting. Saturday was a picture perfect day with about 75 people in attendance. We met at the church for registration with social kick-off with pastries, juice and coffee before we headed on our walk. Some people opted to stay at the church which worked out well to man the registration table and be there when the food arrived.

The lunch was a variety of pita bread sandwiches, salad, miniature gourmet veggies flown in from Ohio (thanks to friends of Julie Auer who are in the business), chips, and a variety of beverages. Our CATW added over \$70,000 for research which is by far the highest amount we have brought in but that is also thanks to the generous Walker-by-Proxy “SPF members/friends” from Iowa, Kentucky and southern California who joined us in spirit.

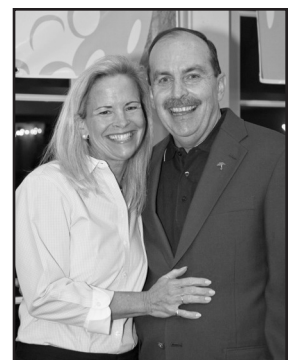
So a very special thanks to Jackie Wellman, Lois Wagoner from Iowa, Lee Anderson from Kentucky and Liz Lepper from southern CA for your fundraising. We proudly “rolled and walked” for you. Also this year we had an extremely generous donation of \$20,000 in honor of one of community members so we did good. See you all next year!



Drive “FORE” SPF

by Annette Lockwood

Although the morning of October 16 started out a bit cold and windy, it turned out to be a beautiful day. Eighty golfers participated and were very generous when it came to raffle tickets for 50/50 plus autographed pin flags (Ian Poulter, Hunter Mahan and Matt Kuchar) and a Movado watch. There were also several silent auction items including an autographed Giants Game Day football and autographed Eli Manning jersey which were provided by Chris Falconer who also attended the reception. Jim (HSP) & Diane Zalewski helped sell raffle tickets to the golfers. Neil Levy (HSP) was also there as his father has been friends with Jim for many years.



Dr. Mitsumoto also joined the group for the reception. After Jim’s wife, Maureen, gave a moving speech, Dr. Mitsumoto spoke to the group about his current research projects.

A wonderful day and the finest tribute to Jim!

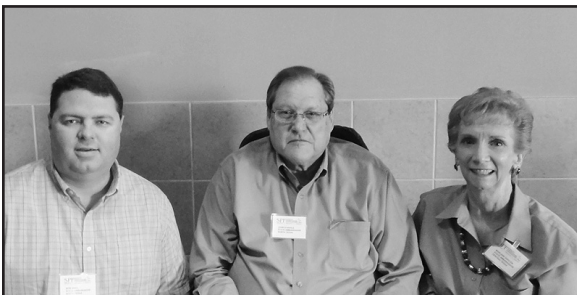


August 25th Austin Patient Connection.

We had a great afternoon with lunch, talking, sharing information, and laughing. We went around the table and introduced ourselves first then conversation began. Information was shared about the Texas Scottish Rite Hospital for Children. It is a new program specifically for children through age 18 who have HSP.

If you are interested in getting information, please let me know. I encourage you to hold a patient connection in your town by emailing your state ambassador to get contact information. State ambassadors are found at www.sp-foundation.org. If your state does not have an ambassador, please email Linda Gentner, lkgentner@aol.com, to get the list of those affected with HSP or PLS in your area.

Marlene Doolen
Texas Ambassador



Texas Ambassadors:

Bob Aniol, South Texas
John Staehle, North Texas
Marlene Doolen, Central Texas

New Pediatric HSP Clinic Opens in Texas

Texas Scottish Rite Hospital for Children has established a pediatric hereditary spastic paraplegia (HSP) clinic which opened in August. This specialized clinic, created in response to the hospital's growing population of patients with



HSP, is focused on devising and implementing new programs that meet the complex needs of patients and their families, with the ultimate goal of improving the diagnosis, management and treatment of HSP for kids around the world.

The clinic is led by Dr. Mauricio Delgado, M.D., medical director of the hospital's Neurology department and expert in neurological and neuromuscular disorders.

Scottish Rite, which is well-known for providing world-class care for children with orthopedic conditions, neurological disorders and dyslexia, is currently conducting research on HSP. A database of children diagnosed with HSP, maintained and funded by the hospital, will assist scientists in investigating the origin, incidence, symptoms and treatment of the disease.

Currently, the database includes information on over 100 children with HSP. In utilizing this information, investigators will be better able to test new ideas and develop treatments for future patients. Scottish Rite researchers are also exploring diffusion tensor imaging (DTI), which is a unique tool used to visualize and characterize white brain matter pathways. Because traditional MRI studies of the brain show few abnormalities in patients with HSP, DTI is an important step forward in research.

Additionally, researchers plan to use whole-exome sequencing to identify new genes associated with early-onset HSP and develop genetic testing standards that will impact the clinical management of patients with early-onset HSP.

Children with HSP are also seen in the hospital's Movement Science Laboratory, which uses motion capture technology to determine how patients move and walk. Walking speed and cadence, three-dimensional joint motions, muscle strength, and plantar pressures under the foot will be measured as part of the research. Through these and other efforts at the hospital, researchers and clinicians are working toward a brighter tomorrow for HSP patients.

For more information about the HSP Clinic or HSP research at Texas Scottish Rite Hospital for Children, please contact Linsley Smith, at 214.559.7698 or Linsley.Smith@tsrh.org.

Research in Motion

Malin's Ekso Exoskeleton Trial

by Malin Dollinger, M.D.

Many of you may have heard of or may be familiar with a robotic walking device, that was originally created for the military, so soldiers could carry heavy loads, but has lately been adapted to allow paraplegics to walk.

It is controlled by its own internal computer, which is programmed for each individual patient. If you do a Google search for "Ekso" you will find information and be able to see the video. It is an exoskeleton, that is it fits around the legs and feet, and straps to your chest, and weighs about 50 pounds.

When fitted and working properly, the machine recognizes from your body movement and learns what you want it to do, and will stand you up from a sitting position, and will tell your legs to move in a walking mode, with your continuous instructions by body posture and leaning, to enable you to walk. The device bears its own weight, so you don't need to lift anything. There have been some amazing and important successes with paraplegics, in particular with spinal cord injuries.

That being said, this device looked so interesting, important, and practical, not to mention useful, that I began a correspondence with the company in Northern California with the aim of trying out the device. It is currently not being sold commercially, but remains in clinical trial.

A few weeks ago I spent an hour with a designated physiatrist (*a physical medicine doctor*), to see if I would qualify for a formal trial. He took many measurements of range of motion and strength and send his report to the company who accepted me into their trial.

On arrival, I was greeted by a team of six physical therapists, including one from the Ekso, who spent an hour making even more complete and elaborate measurements of my strength and range of motion, my legs in particular. There were some limitations of range of motion of my right lower leg. After they had a 15-minute private conference, I was told that they would do the trial then and there.

I was greeted by a large black complex contraption, that wrapped around my legs, needed to have many adjustments made to fit my body, and had knee pads, foot plates, abdominal binder, shoulder straps, and various other fastening devices, all tailored to me.

Once the apparatus and my body were "assembled," there was no voluntary movement possible unless the on-board computer was told to do so, either by the therapist or my me. They placed a large heavy-duty walker around me, to hold onto. After much time was spent making adjustments, it was time for me to stand up. They told me what to do, and what not to do, and in phase one, they control the computer. They told the device to "Stand up!" and so it did, with me inside.

Then, in the standing position, they made more measurements of range of motion of my lower legs. At that moment, I realized, and they confirmed, that because of the slight limitation of the range of motion of my lower legs, I would not be able to use the device, because I could not make its computer understand and respond to my too-limited motions.

I give them great credit and appreciation for their time, energy, and expertise. They were kind, courteous, and always reminded me that they were there to help me and to protect me from any injury. What happens if I fall in this contraption during the test you ask? Not possible: the

whole thing is fastened to a steel track overhead, like a rock climber or a gymnast or diver practicing.

I've had HSP for some 20 years, which is enough time for scarring in the muscles to occur, with limitation of the range of motion. This is the telling reason why this did not work for me. This is why I recommend getting regular physical therapy. It keeps your muscles "loose" and non-contracted.

They intend to produce the Ekso Exoskeleton commercially sometime next year. but there are designated physical therapy facilities, around the country, who have one on hand for clinical trials. They now cost \$150,000 each, with a maintenance agreement costing \$10,000 a year. Of course, we don't have any idea what the final cost will be when marketed; I would hope it might be a third or at most, half that cost.

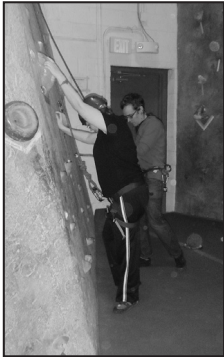


Exercise & You

ADAPTIVE SPORTS

My First Rock Climbing Experience

by Tracy Scott



In 1991, I started a To Do List of things I wanted to do before I died. From then on I have been putting more and more things on that list. One day, I found an indoors rock climbing place in Alexandria, VA. I shared what I had found with my parents and we set Tuesday, October 9, 2012, as the day I would be going rock climbing. I was so

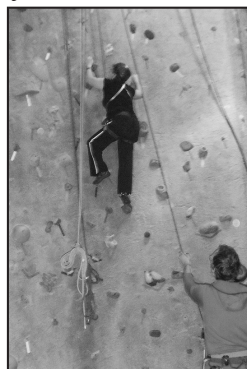
excited and not too sure what to expect.

My father opened the door at Sport Rock and my eyes opened wide. There were rock walls everywhere. I smiled. I put these shoes on, helmet on my head, and got all strapped in. The instructor and I went over to a beginner wall. I started up the wall. My left arm started hurting from a car accident I was involved in. I looked over to my mother and shook my head. She knew I was finished.

But I was not finished! I was determined to make it to the top. My father got all strapped in, helmet on and went like Spiderman up the wall. Then my mother tried. She managed to get half way up and she was finished. The instructor looked at me and I shook my head, stood up, grabbed my walker and walked over to him on the mat. The instructor added a few rocks to the wall.

Then it was my turn again. No looking back now. I started up that wall and made it to the top! I am so proud of myself for not giving up. Now I am looking forward to doing more things on my To Do List.

Just because we may be different than others does not mean we cannot do the things they do! It just means we will do it when we are ready. You can do whatever you want. Some assistance may be required, but follow your dreams. Do not let fear stop you! You *can* do it!



Horses, Kids & HSP

by Kim Madden

My son has been doing horseback riding (hippotherapy) since he was two. It's an amazing sport. He has help getting on the horse and two people who walk on either side of him and one who leads the horse because he's still quite small, and of course horseback riding can be dangerous too (he once had a jumpy horse and they got him off of there super quick).



There are photos of him all over the website of the place he goes Flying Manes in the Bronx (including a bunch of articles and videos about him under the "About us" tab after the Yankees came to visit the horseback riding program -- unfortunately they said he had CP not HSP but anyway he had a great time!).

Horseback riding is one of his favorite things to do, plus it's really good for stretching out his adductors and strengthening his core. It's hard sometimes to get him on and off a horse depending on how tight he is but he really loosens up afterwards and even more importantly he has a great time doing it -- it's a lot more fun than PT!



12 year old Ashleigh Gladde proudly displays her ribbons for 1st place in Pleasure Riding, 2nd place for Equestrian Riding & 2nd place for Trail Riding! She is in Special Olympics Horseback Riding.

HSP Research: The Promise and the Reality

NIH Finding Novel Ways to Understand Genetics Diseases

Editor's Note: This article has been heavily edited for length. Please visit <http://www.nih.gov/news/health/sep2012/od-05a.htm> to read the entire version.

Researchers supported by the NIH Common Fund have discovered that genetic differences linked to a wide variety of diseases, including many adult-onset diseases, influence how genes are activated during fetal development.

These findings may help to explain why some environmental exposures in utero or during early childhood are known to increase risk of diseases that produce symptoms years or even decades later.

In addition, researchers were able to pinpoint which cell types are affected by different diseases. These results provide new insight into disease mechanisms, and suggest novel targets for therapeutics development and disease prevention strategies.

“These findings can potentially lead to a new understanding about the mechanisms of many common diseases, such as cancer, cardiovascular disease, diabetes, and neurological disease, as well as normal variation in physical traits,” said NIH Director Francis Collins, M.D., Ph.D.

Senior author John Stamatoyannopoulos, M.D., and colleagues report their findings in the Sept. 5 online issue of the journal *Science*.

Scientists have previously used genome-wide association studies (GWAS) to look across the DNA of many people and identify genetic differences, or variants, associated with different diseases. However, the overwhelming majority of GWAS variants are not located within genes themselves, but are in stretches of DNA between genes, called non-coding DNA. These non-coding regions were once considered to be mostly non-essential, but it is now known that these regions have important roles in regulating how, where, and when genes are expressed.

A major challenge in GWAS studies has been difficulty in linking variations in non-coding regions with the genes they regulate, because the target genes can be located a great distance away. In the current study, researchers were able to look across the genome and identify which genes were regulated by hundreds of GWAS variants, including variants associated with blood platelet counts, amyotrophic lateral sclerosis (ALS), Crohn's disease, breast and ovarian cancer, and schizophrenia.

In the current study, 79 percent of GWAS variants in regulatory DNA were connected to genes that were not the closest ones to the variant, underscoring why previous efforts to link GWAS variants with target genes have been so difficult.

“These exciting results show how a broad, systematic approach to deciphering regulatory DNA — essentially the genome's operating system — can have major implications for our understanding of the genetic basis of many common diseases and traits,” said Dr. Stamatoyannopoulos, associate professor of genome sciences at the University of Washington.

Researchers also determined that GWAS variants from similar diseases often disrupted interconnected networks of proteins. GWAS variants associated with a group of autoimmune diseases were found to disrupt a distinct set of proteins, and this set of proteins was different from the sets of proteins affected by GWAS variants associated with neurological diseases and various cancers.

Disruption of these common regulatory protein networks may explain why seemingly unconnected GWAS variants can be associated with closely related diseases that share overlapping symptoms.

“The fact that susceptibility to many diseases can be traced to variants that affect common regulatory networks opens the door to a greater understanding of the roles that different genes and regulatory elements play in health and disease, and should enable new approaches to disease diagnosis, treatment, and prevention,” said Stamatoyannopoulos.

SYNAPSE APPEAL

Synapse costs lots of money to print and mail, and we need your help to keep it going for another year. Please use the enclosed response envelope to make a donation. Every little bit helps.

Up Close and Personal

SPF members go to school

Sherry Vinson and Dave Irvine had the honor of attending and speaking to Professor Kristie Spencer's graduate speech therapy students at the University of Washington. There were 42 students in attendance who will become speech language pathologists.

The students were learning about dysarthria. We introduced them to primary lateral sclerosis and the SPF. After we told our "stories" we were asked about our lives prior to PLS and about how we were diagnosed, as well as the progression that left us with speech difficulties.

Being a bit nervous, I was glad to have Sherry there for support. Professor Spencer gave us a very nice introduction and made it easy to begin. We both told the short versions of our stories and traded off speaking. There was a Q&A session after the first hour and the students were very interested and had good questions.

I believe that the main thing we were able to convey to them was how difficult it is to lose one's voice and how communication has changed for us and everyone we come into contact with. I think we were also able to leave a lasting impression of how important they will be in their patient's lives.

We also did a bit of show and tell. I recently had a soft palate lift, or palatal lift prosthesis made. It looks like a retainer that has an extension in back that holds the soft palate up which prevents air escaping through my nose making my speech less nasal sounding. The students had never seen one and I related the process of having it made, which was one of the harder tasks I have been through.

Sherry had recently purchased an iPad and software called "Speak It." She also brought her service dog and best pal, Luc. You can read Sherry's blog (<http://primarylateralsclerosis.org/>) for a more detailed version of the class. I would say everyone learned a lot and it was a very good experience for all.

David Irvine
Washington State Co-Ambassador



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Research Sound Bytes

Neuralstem Using Stem Cells in ALS

A company called Neuralstem, Inc. has developed a technology that allows large-scale expansion of human neural stem cells (hNSC) from all areas of the developing human brain and spinal cord. Management is currently focusing the company's efforts on replacing damaged, malfunctioning, or dead neural cells with fully functional ones that may be useful in treating many central nervous system diseases and neurodegenerative disorders.

Neuralstem's lead development program is for amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, named after the famous New York Yankee first baseman who was diagnosed with the disease in 1939, and passed in 1941 at the age of only 37.

Neuralstem is seeking to treat the symptoms of ALS via transplantation of its hNSCs directly into the gray matter of the patient's spinal cord. In ALS, motor neurons die, leading to paralysis. In preclinical animal work, Neuralstem cells both made synaptic contact with the host motor neurons and expressed neurotrophic growth factors, which are protective of cells.

All patients its Phase I trial in 2010 tolerated the treatment without any long-term complications related to either the surgical procedure or the implantation of the stem cells. This was clearly an encouraging sign, and a key hurdle cleared.

Results from the first twelve patients were presented at the American Neurological Association annual meeting in September 2011. Clinical assessments ranging from 6 to 18 months after transplantation demonstrated no evidence of acceleration of disease progression due to the intervention.

Results even show that one patient demonstrated improvement in his clinical status, though these data must be interpreted with caution since this trial was neither designed nor powered to measure treatment efficacy to statistical significance.

Neuralstem's approach uses human spinal stem cells that, once injected, can provide multiple mechanisms of action on multiple pathways to affect the disease. Plus, Neuralstem's approach is highly targeted, with the cells injected directly into the lumbar or cervical spine. Following grafting, the hypothesis is that the cells rebuild circuitry with the patient motor neurons and protect existing neurons from further degradation.



Rice Univ. Gets \$1.4M to Probe Atlastin

Rice University biochemist James McNew has gotten used to doing research on the fly, but he no longer has to do it on a shoestring thanks to a new grant from the National Institutes of Health (NIH).

The new four-year \$1.4 million R01 grant is for the study of a protein called atlastin, a key player in the genetic disorder hereditary spastic paraplegia (HSP). In going after the grant, McNew, associate professor of biochemistry and cell biology, abandoned his laboratory's long-standing model organism — single-celled yeast — in favor of studying fruit flies.

"It's a relief to finally have some dedicated funding for this," McNew said. "This grant gives us the ability undertake some of the more in-depth investigations into atlastin that we've had our eye on for a while."

McNew said he hopes the study of atlastin will reveal new clues about HSP and perhaps point to new ways of treating it. As many as 40 defective genes have been linked with HSP, but one gene in particular has been linked to as many as 10 percent of all HSP cases. That mutation is to the gene that produces atlastin, and McNew's lab is one of a handful worldwide trying to find out how atlastin works and why atlastin defects cause HSP.

For McNew, the quest to untangle atlastin's mysteries began about four years ago with a phone call. "Andrea Daga called me from the Medea Institute (in Italy) to see if our group could apply some of our methods to determine whether atlastin could cause membrane fusion," McNew said.

At the time, McNew's lab studied SNAREs, proteins that act something like a loading dock manager to help regulate the flow of "cargo" through the cell's internal membrane

system. SNAREs are one of the few proteins that can promote membrane fusion, a process that leads to the formation of tiny, temporary doorways through the cell's membranes.

Daga asked for McNew's help in studying atlastin because some of its traits suggested it might also be a membrane fusion protein. The pair confirmed that to be true in 2009, and they have continued collaborating to piece together a bigger picture of how atlastin works.

"We discovered that atlastin plays a key role in building and maintaining an important internal compartment of healthy cells called the endoplasmic reticulum (ER)," McNew said.

That find was critical because HSP affects the longest cells in the body, upper motor neurons. It is possible that defective atlastin leads to ER defects, and if that's true, the effects are more likely to appear in long nerve cells that have lots of ER.

For now, that's still a hypothesis, and McNew said the new grant will help him and his students find some of the evidence needed to test the hypothesis. For example, McNew's group at Rice's BioScience Research Collaborative will investigate the basic mechanism that atlastin uses to fuse together pieces of the ER.

In one series of experiments, they will create a number of mutant atlastin proteins, each with a defect designed to make the protein malfunction in a specific way. By studying how each of these mutations affects the ability of atlastin to drive membrane fusion, the team hopes to build up a better understanding of how healthy atlastin does its job.

"If we can find some of the answers to how atlastin works, it could answer some fundamental questions about HSP," McNew said.

Are alsin and spartin novel interaction partners?

Cobanoğlu G, Ozansoy M, Nazlı Başak A.

Source: Department of Molecular Biology and Genetics, Neurodegeneration Research Laboratory (NDAL), Boğaziçi University, Istanbul, Turkey.

Mutations in ALS2 gene/alsin are associated with recessive forms of motor neuron disorders including Juvenile Amyotrophic Lateral Sclerosis (JALS), Infantile-onset Ascending Hereditary Spastic Paraplegia (IAHSP) and Juvenile Primary Lateral Sclerosis (JPLS). In this study, we show that alsin and another MND-linked protein, spartin are related to each other both at mRNA and protein

levels in Neuro2a cells. We observed significant alterations in spartin expression in alsin knock-down conditions. We further found that both proteins colocalize in N2a cells and spartin isoform-a precipitates with alsin in the same protein complex. In the light of these results we suggest that alsin and spartin may interact each other physically.

Knockdown of pnpla6 protein results in motor neuron defects in zebrafish.

Song Y, Wang M, Mao F, Shao M, Zhao B, Song Z, Shao C, Gong Y.

Source: Shandong University, Jinan, Shandong, China.

Mutations in patatin-like phospholipase domain containing 6 (PNPLA6), also known as neuropathy target esterase (NTE), or SPG39, cause hereditary spastic paraplegia (HSP). Although studies on animal models including mice and *Drosophila* have extended our understanding of PNPLA6, its role in neural development and HSP is not clearly understood. Here, we generated a vertebrate model of PNPLA6 insufficiency using morpholino oligonucleotide knockdown in zebrafish (*Danio rerio*). PNPLA6 knockdown results in developmental abnormalities and motor neuron defects including axon truncation and branching. The phenotypes in *pnpla6* knockdown morphants can be rescued by introduction of wide type (WT), but not mutant, human PNPLA6 mRNA. Our results also revealed the involvement of BMP signaling in *pnpla6* knockdown phenotypes. Taken together, these results demonstrated an important role of PNPLA6 in motor neuron development and implicated overexpression of BMP signaling as the possible mechanism underlying the developmental defects in *pnpla6* morphants.

KIF1A missense mutations in SPG30

Klebe S, Lossos A, Azzedine H, Mundwiller E, Sheffer R, Gausson M, Marelli C, Nawara M, Carpentier W, Meyer V, Rastetter A, Martin E, Bouteiller D, Orlando L, Gyapay G, El-Hachimi KH, Zimmerman B, Gamliel M, Misk A, Lerer I, Brice A, Durr A, Stevanin G .

Source: INSERM, U975, Paris, France.

The nosology of autosomal recessive forms of HSP is complex as most mapped loci have been identified in only one or a few families and account for only a small percentage of patients. We used next-generation sequencing focused on the SPG30 chromosomal region on chromosome 2q37.3 in two patients from the original linked family. In addition, wide genome scan and candidate gene analysis were performed in a second family of Palestinian origin. We

identified a single homozygous mutation, p.R350G, that was found to cosegregate with the disease in the SPG30 kindred and was absent in 970 control chromosomes while affecting a strongly conserved amino acid at the end of the motor domain of KIF1A. Homozygosity and linkage mapping followed by mutation screening of KIF1A allowed us to identify a second mutation, p.A255V, in the second family. Comparison of the clinical features with the nature of the mutations of all reported KIF1A families, including those reported recently with hereditary sensory and autonomic neuropathy, suggests phenotype-genotype correlations that may help to understand the mechanisms involved in motor neuron degeneration. We have shown that mutations in the KIF1A gene are responsible for SPG30 in two autosomal recessive HSP families. In published families, the nature of the KIF1A mutations seems to be of good predictor of the underlying phenotype and vice versa.

Phosphoinositides differentially regulate protrudin localization through the FYVE domain.

Gil JE, Kim E, Kim IS, Ku B, Park WS, Oh BH, Ryu SH, Cho W, Heo WD.

Source: Korea Advanced Institute of Science and Technology, Korea, Republic of;

Abstract: Protrudin is a FYVE (Fab 1, YOTB, Vac 1 and EEA1) domain-containing protein involved in transport of neuronal cargoes and implicated in the onset of hereditary spastic paraplegia (HSP). Our image-based screening of lipid binding domain (LBD) library revealed novel plasma membrane (PM) localization of the FYVE domain of protrudin unlike canonical FYVE domains that are localized to early endosomes. The membrane binding study by surface plasmon resonance (SPR) analysis showed that this FYVE domain preferentially binds phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P(2)), phosphatidylinositol-3,4-bisphosphate (PtdIns(3,4)P(2)) and phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P(3)) unlike canonical FYVE domains that specifically bind phosphatidylinositol-3-phosphate (PtdIns(3)P). Furthermore, we found that these phosphoinositides (PtdInsP) differentially regulate shuttling of protrudin between endosomes and PM via its FYVE domain. Protrudin mutants with reduced PtdInsP-binding affinity failed to promote neurite outgrowth in primary cultured hippocampal neurons. These results suggest that novel PtdInsP selectivity of protrudin-FYVE domain is critical for its cellular localization and its role in neurite outgrowth.

The Endoplasmic Reticulum: A Social Network in Plant Cells.

Chen J, Doyle C, Qi X, Zheng H.

Source: State Key laboratory of Tree Genetics and Breeding, Research Institute of Forestry, The Chinese Academy of Forestry, Beijing 100091, China Department of Biology, McGill University, 1205 Dr. Penfield Avenue, Montreal, Quebec, H3A 1B1, Canada.

Abstract: The endoplasmic reticulum (ER) is an interconnected network comprised of ribosome-studded sheets and smooth tubules. The ER plays crucial roles in the biosynthesis and transport of proteins and lipids, and in calcium (Ca²⁺) regulation in compartmentalized eukaryotic cells including plant cells. To support its well-segregated functions, the shape of the ER undergoes notable changes in response to both developmental cues and outside influences. In this review, we will discuss recent findings on molecular mechanisms underlying the unique morphology and dynamics of the ER, and the importance of the interconnected ER network in cell polarity. In animal and yeast cells, two family proteins, the reticulons and DP1/Yop1, are required for shaping high-curvature ER tubules, while members of the atlastin family of dynamin-like GTPases are involved in the fusion of ER tubules to make an interconnected ER network. In plant cells, recent data also indicate that the reticulons are involved in shaping ER tubules, while RHD3, a plant member of the atlastin GTPases, is required for the generation of an interconnected ER network. We will also summarize the current knowledge on how the ER interacts with other membrane-bound organelles, with a focus on how the ER and Golgi interplay in plant cells.

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EURORDIS — European Rare Diseases Organisation on RareConnect (<http://www.eurordis.org>)

— An international community for HSP in 5 languages, there are some interesting stories there from Spain and Norway. Please consider registering and adding your news and stories to share with the rest of the world. The more people that get involved the better off we all will be.