2020 was a very important building block year for The Spastic Paraplegia Foundation. As with every person and organization, COVID-19 made things a great struggle. When COVID began, many of us were afraid of what would happen to your giving but you stepped up to the challenge and 2020 was our best fundraising year yet. Thank You!! As always, these added funds translate into our being able to support even more world’s best upper motor neurological research. The day when people with HSP and PLS can easily be diagnosed treated and cured is even closer. As you know, our Annual Conference turned into a Virtual Conference and we were able to speak to people all over the world. Today, our foundation serves people on every continent on this planet and we support research of scientists all over the world as well. Let me tell you about just some of the highlights of the progress that is taking place with the research we are sponsoring, with your generous support.

Frank Davis
SPF President

Research and Developments

Thanks to You! Dr. Morfini is getting so close to developing treatments for SPG4 HSP

Understanding How Mutant Spastin Affects the Intracellular Movement of Organelles

Gerardo Morfini, Ph.D.
University of Illinois

Most neurons have a cell body, multiple dendrites, and a long cytoplasmic projection termed axon that extends to their target cells. Axons transmit electrical information from a neuron to another in a manner analogous to man-made electrical wires. But unlike such wires, axons feature hundreds to thousands of specialized subdomains, including nodes of Ranvier and presynaptic terminals, which allow inter-neuronal communication.

Upper motor neurons, the main cell type affected in Hereditary Spastic Paraplegia (HSP), bear some of the longest axons in the human body. Extending over a meter in length in some cases, these axons connect neuronal cell bodies in the cerebral cortex to their target cells in the distant spinal cord (corticospinal axons). It is well established that the clinical symptoms of HSP results from degeneration of these axons, but mechanisms underlying this degeneration remain elusive. An illumination of such mechanisms might inspire novel therapeutic strategies to treat SPG4-HSP by preserving axonal connections.

Because the protein synthesis machinery is located in the cell body of neurons, all cellular organelles (i.e. mitochondria) and protein components needed to sustain
axonal health have to be transported over long distances from their site of production. This cellular process, referred to as axonal transport, is executed by molecular motor proteins. By allowing the sustained delivery of molecular components to axons, axonal transport plays an essential role on the ability of neurons to receive, process and transmit information. Interestingly, some HSP variants are caused by mutations in genes encoding molecular motors. This genetic evidence reveals that upper motor neurons are uniquely vulnerable to deficits in axonal transport.

Mutations in multiple genes have been found to cause HSP. Among those, mutations in the SPAST gene account for the majority of HSP cases. The SPAST gene encodes a protein termed spastin, which is involved in severing of microtubules, cytoskeletal elements that provide structural support to axons. For a long time, it was thought that HSP forms associated with SPAST mutations (SPG4-HSP) resulted from deficits in spastin, but how such deficits would promote degeneration of corticospinal axons was not obvious.

A major challenge in HSP research is to reveal mechanisms linking mutations in SPAST to degeneration of corticospinal axons. Based on the well-established dependence of axons on appropriate axonal transport, they set out to determine whether mutant spastin proteins interfere with axonal transport and to reveal the underlying mechanisms.

Results from our work showed that mutant spastin proteins indeed inhibit axonal transport. Interestingly, this toxic effect involved aberrant activation of an enzyme termed casein kinase 2 (CK2), which inhibits the function of molecular motor proteins. Collectively, findings from our work revealed a novel mechanism linking mutations in the SPAST gene to aberrant CK2 activation, deficits in axonal transport and degeneration of corticospinal axons in HSP. These findings suggest that pharmacological inhibition of CK2 might represent a novel therapeutic strategy to preserve corticostriatal axons and prevent the onset of disease symptoms associated with this event in SPG4-HSP.

Identification of the Neuronal Transcriptomic Signature Associated With Lysosomal Defects in Hereditary Spastic Paraplegia SPG11

Typhaine Esteves, Liriopé Toupenet, Julien Branchu, Frédéric Darios, Daniel Stockholm and Giovanni Stevanin, Institut du Cerveau, Pitié-Salpêtrière Hospital, Paris, France

SPG11 is one of the most frequent forms of hereditary spastic paraplegia in many countries.

This frequent subtype of spastic paraplegia is caused by alterations of the genetic information encoded by a portion of human chromosome 15 present in all cells of the body, namely the SPG11 gene. This gene is a chromosomal region responsible for the production of one protein important for recycling mechanisms in the cells. However, we still do not know why the loss of synthesis of this protein leads to the clinical symptoms in patients. Establishing the links between this protein and the clinical symptoms in patients is a prerequisite to identify a therapeutic target.

One way to understand the mechanisms occurring in the cells in patients is to reproduce the disease in animal models. They have reproduced the disease in a mouse model by genetic engineering and they observed that before symptoms appear, there is a specific accumulation of lipids in cellular compartments...
of the cells involved in recycling. The project funded by SPF was to determine what are the deregulations in the cells leading to these abnormal lipidic accumulations and to the clinical symptoms.

To do so they have analyzed the expression of all proteins/genes encoded by the mouse chromosomes in the brain of these SPG11 mice using a technique called transcriptomics. The idea is to determine what differs in protein production between cells affected or not by SPG11.

They observed specific deregulations in mice affected by the disease compared to healthy mice. First, many genes, and then the proteins they code for, are involved in degradation/recycling functions in cells which fits what we know about the function of the protein encoded by SPG11. In addition, close to 30% of the genes whose expression is reduced or increased are encoding enzymes involved in the synthesis or degradation of lipids, again in agreement with what we know about the pathological process. Finally, there are genes involved in inflammation that are also affected in late stages of the disease suggesting that this process participates in the severity of the disease.

This project is far from the end. Now that they have established the profile of protein/gene expression in the brain of mice affected by SPG11, they need to validate the findings in vitro by modulating the expression of these protein/genes, one by one, in cells from SPG11 mice and check if they can increase or decrease the severity of lipid accumulation and cell suffering. Some of the up or down expression of proteins are probably due to compensatory mechanisms while others are deleterious, including those affecting the inflammation. Genes whose expression modulation will affect lipid accumulations and cell suffering in vitro will represent good targets for therapeutic intervention. This work is ongoing and they hope that several of these deregulations will give them opportunities to compensate the abnormal mechanisms ongoing in cells of human patients and in the mouse model.

Thanks to You!! Dr. Baas has almost ready to treat SPG4 HSP!

**Using Mice to Understand the Cause of SPG4 Hereditary Spastic Paraplegia and Develop New Treatments**

*Peter Baas Ph.D., Drexel University College of Medicine, Philadelphia PA*

Dr. Baas’ laboratory studies the most common variant of Hereditary Spastic Paraplegia, which is caused by mutations of the SPAST gene. This variant of the disease is called SPG4-HSP. SPAST encodes for a protein called spastin. Similar to other variants, the patients suffer from spasticity and gait deficiencies due to corticospinal dying-back degeneration. The condition is usually adult-onset, but it can be any age. SPAST encodes a protein called spastin, which is a microtubule-severing enzyme that also has membrane-related functions. Microtubules are architectural elements whose lengths must be carefully regulated in nerves in order to carry out their functions. Microtubules act as railways for the transport of organelles and proteins down the length of the nerves. Dr. Baas’ goals are to learn whether the disease symptoms are mostly caused by spastin’s normal function being compromised (“loss of function”) or by the mutant protein causing problems (toxic “gain of function”). To do this, they developed a mouse model in which they have introduced human mutant spastin and they also developed cell culture models in which they are able to delve deeper into what’s wrong with the underlying cellular pathways.

Their goals in learning more on this matter are to develop therapies that prevent the symptoms from getting bad in the patients or even reverse the symptoms in patients who are already suffering. Their approach is to study mice (or cells in culture) that only have the loss of spastin’s normal function or only
have the problems caused by the mutation. This way they can discover which symptoms relate to each one and then develop therapies that address each one.

Putting the two together, they can then develop a treatment regimen for patients. Much of their work revolves around a structure inside nerve cells called the microtubule, and this is because spastin is a protein that normally regulates microtubules. Interestingly, they postulate that both aspects of the disease they are studying separately converge on microtubules, and hence that microtubule biology might be the key to understanding both the disease and the best possible therapies.

Shown schematically here, from a recent publication by Drs. Baas and Qiang, is their hypothesis on how loss-of-function (i.e. haploinsufficiency) and gain-of-function (i.e. toxic mutant effects) contribute to degeneration of the corticospinal nerve tracts in SPG4-HSP (upper panel). The explanation can also potentially explain cases in which the SPAST gene is entirely deleted because the reduced spastin could make the nerves vulnerable to mutations in other genes (lower panel).

We are grateful for the funding that we have received from the Spastic Paraplegia foundation to seed these studies. Those funds have enabled us to earn significant additional funding for the project from the National Institutes of Health.

Thanks to You!! Dr. Mitsumoto is getting PLS ready for Clinical Trials.

Primary Lateral Sclerosis, Natural History Study

Hiroshi Mitsumoto M.D. DSc, College of Physicians and Surgeons Columbia University Neurological Institute

Primary Lateral Sclerosis (PLS) is classified as a motor neuron disease, which is generally defined as a rare neurodegenerative disease. PLS attacks only the upper motor neurons, which are present in the brain. When lower motor neurons residing in the brainstem and spinal cord are simultaneously affected, the disease is called Amyotrophic Lateral Sclerosis (ALS), which has a much faster and fatal disease course. PLS is very rare. Out of 100 patients with ALS, roughly two or three patients turn out to have PLS. PLS causes slowly progressive motor dysfunction in walking, hand dexterity, speech, and swallowing in adults, resulting in lifelong disability and hardship.

Because of its rarity, we cannot study a large number of patients by ourselves. It is crucial to assemble many study sites that can work together on the same protocol and recruit the necessary number of participants so that we are able to conduct a statistically-sound study. It is also true that PLS has never been
included in any clinical trials designed for ALS for sensible reasons. While ALS and PLS share similar clinical features, PLS differs from ALS, because it progresses at a much slower pace. This has prevented the simultaneous investigation of these diseases. For example, researchers use the ALS Functional Rating Scale-Revised (ALSFRS-R), which is the most broadly used and tested clinical scale to evaluate disease progression in ALS. We found that the ALSFRS-R lacks the sensitivity to detect the slow changes that characterize PLS. We realized that we need a new disease scale for PLS. As a result of the generous support received from The Spastic Paraplegia Foundation, we developed a novel clinical scale called the PLSFRS (PLS Functional Rating Scale) by modifying the ALSFRS-R. With this new scale, we have demonstrated that we can detect significant changes in the disease progression of PLS in a period as short as 6 months; the results of which have been provided in our published manuscript.

With this project, Dr. Mitsumoto proposes to study the natural history of PLS, specifically how the disease progresses in the majority of patients. This is an ideal time for such a study, because they do not have any approved medications for the treatment of PLS yet. Furthermore, they lack detailed data about the natural history of PLS. Information regarding how the disease evolves and progresses is essential to designing effective clinical trials. Such investigations have never been carried out in the past. Additionally, the past diagnostic criteria for PLS required a waiting period of at least 3 to 4 years after symptom onset before a diagnosis could be made. Dr. Mitsumoto organized an international meeting of world-renowned investigators, who worked diligently to establish new PLS diagnostic criteria. With these new criteria, they are now able to make a diagnosis of “probable” PLS much earlier in the disease course (at least two years following symptom onset). Although they plan to study patients with “definite” PLS (at least four years following symptom onset), they also want to investigate patients in earlier stages of the disease (before four years of symptom onset). The main reason why they want to investigate patients during this time is because medications that are potentially beneficial for patients with PLS may be most effective in the early stages of the disease when motor neurons are still well-preserved and functioning. The medication should be initiated during these earlier stages; thus, collecting natural history data before two years is critical.

Accomplishing their study goals despite the limitations is a challenge. First, they must organize and coordinate the collaboration of 32 study sites located throughout the USA and Canada, who have expressed interest in participating in this study. They will ask them to enroll participants with two types of diagnoses: 1) 50 participants with early PLS (symptoms less than 4 years after symptom onset, including probable PLS) and 2) 50 participants with definite PLS (at least 4 years after symptom onset). The study site will be allowed to enroll as many patients as possible since this is such a rare disease. They hope to enroll all participants within one year and follow them for a duration of two years. They will ask all sites to perform an identical examination; administration of an upper motor neuron scale (detecting changes of upper motor neuron signs); vital capacity assessment; and recording of the time it takes for the participant to stand from being seated, walk 3 meters, and then return to sit on the same chair. They will collect DNA and blood samples; therefore, we will be able to exclude any participants who have a known genetic cause of motor neuron disease that resembles PLS. Further, they will establish a biorepository for future biomarker development. The Columbia research team will call the study participants every three months to assess medications taken during the disease course and assess use of durable

INFORMATION REGARDING HOW THE DISEASE EVOLVES AND PROGRESSES IS ESSENTIAL TO DESIGNING EFFECTIVE CLINICAL TRIALS.
medical equipment, which will indicate over-all disability status. Further, they will administer the PLSFRS, a new functional disability scale (ROADS), Neuro-QOL, and a quality of life assessment. They will also measure how fast the participant can enunciate and repeat ‘Pa-Ta-Ka’ and tap their fingers (thumb and index finger) and feet against the floor via video conference call.

Their goal is to make PLS amenable and accessible for effective clinical trials. They will collect data on how the disease progresses for one year using identical outcome measures for all patients who participate in the study. Their biostatistician can analyze data on disease progression rate from these specific measures. From these analyses, they will determine which measure is most reliable and ideal for use in future clinical trials. Further, we will know how many patients we will need to design a new clinical trial. After the current project, they should be able to move forward in initiating a clinical trial, since potential medications have been introduced for the treatment of PLS. They have an additional goal with this project. They will follow patients with early PLS and well-established PLS. At the end of the 12-month follow-up period, they will obtain EMG testing to determine if the patients’ initial diagnosis of PLS (early, probable and definite) made at the baseline session is still correct 12 months later. These results will provide information on the reliability of the newly published PLS diagnostic criteria at 12-month follow-up.

A project of this magnitude is very expensive. It has been funded by multiple funding agencies, including The Spastic Paraplegia Foundation, the ALS Association, Mitsubishi Tanabe Pharma, a private donation by Mr. David Marren and his family, and a small grant from MDA Wings. It took nearly one year to negotiate and accumulate the funds necessary to cover the costs of the project. While they have been working diligently to fundraise, they have also been developing the project. It has been almost a year since they received the SPF grant. Although real results may have been expected, this project is a colossal task. They held the first investigators’ meeting in August/September 2020. Columbia University must have a budget agreement and subcontract with each of the sites (a total of 32 sites). Each site must also obtain its own IRB approval, which necessitates center-specific requirements. They have to resolve all questions and issues prompted by each IRB for the study sites. All administrative processes require an enormous amount of time. Almost half of the sites have established a subcontract with Columbia University, and only 20% of the total have obtained IRB approval so far.

The data derived from their entire study will be managed by NeuroBank, Mass General Hospital and Harvard University. They want to share the data with any researchers in the future. NeuroBank is best equipped for this task. They have developed and compiled Case Report Forms for the entire data collection. Each form must be fully reviewed and approved by NeuroBank and the Columbia University IRB. Furthermore, the procedure for blood specimen collection and storage of DNA and plasma samples need to be determined. Following this painstaking work, they will be able to organize another investigators/coordinators meeting very soon to train all evaluators (hopefully within the next 3 months).

Thanks to You!! Dr. Sondermann is getting close to treating SPG3A HSP!!

**Discovery of Novel Mechanisms Underlying SPG3A Hereditary Spastic Paraplegia (HSP)**

Dr. Holger Sondermann, Ph.D. & Dr. Carolyn Kelly, Ph.D. Candidate in Biochemistry Department of Molecular Medicine, Cornell University

Over a decade ago, Dr. Sondermann and his team began studying a protein called atlastin (abbreviated as ATL), which is mutated in...
patients with hereditary spastic paraplegia (HSP) type SPG3A. Currently, treatment for HSP is limited to lessening the symptoms, such as muscle spasticity, while a therapeutic treatment to target the cause of the disease has not yet been discovered. The benefit of developing a treatment that would specifically target the cause of the disease lies in the potential to stop progression of symptoms over time. When researchers are trying to develop a targeted drug or treatment, it’s extremely useful to know as much as possible about what isn’t working properly in the cell. An analogy would be if a person were trying to repair a malfunctioning car, it is much easier to fix the problem if they know what isn’t working and how that broken part affects the car’s ability to function normally.

With this in mind, Dr. Sondermann and his students have focused their research on determining what kind of work ATL carries out in the cell and, more specifically, how it carries out this work on a molecular level. To do this, they have looked at both the “normal” protein (also referred to as the “wild-type” protein) that is present in non-affected people in addition to mutated versions that have been found in a number of HSP patients. By studying the wild-type ATL protein, they have learned a lot about how the protein carries out its job in the cell, and by studying the mutated versions of ATL, they can shed light on how it behaves when it isn’t working as expected. The outcome of having malfunctioning proteins in the cells can be variable, depending on the type of change that is incorporated into the protein. Effects range from “simple” loss of function due to an unstable protein or a protein that acts as if it would not be there to a reduced or enhanced function of some variants. While some outcomes can be predicted based on prior knowledge, more often it is imperative to study the specific protein variants to determine their mode of action.

Another fundamental question that remains to be answered is how the inherited mutations found in HSP patients actually cause the symptoms of the neurological disorder. In the cell, ATL’s main job is to help maintain the structure and shape of an organelle, a specific compartment in cells, called the endoplasmic reticulum (ER). HSP-associated variants of ATL change the structure and function of the ER, yet HSP-related disease symptoms are caused by degeneration of motor neurons. To complicate matters, there are three distinct versions of ATL in cells, with two of the three having been linked to familial disorders. Whether the different ATL versions have redundant or specialized roles in the cells is an active area of research.

As they continue to uncover and understand ATL’s roles in cellular health, they are confident more light will be shed on how ATL’s role in the cell translates to maintaining neuronal health. Recent studies in the Sondermann lab have focused on two general areas of ATL research. In particular, they worked in collaboration with a clinician who has a patient with HSP who carries a mutation in the ATL gene. This mutation was of particular interest because it had never been reported before. Dr. Sondermann and a Ph.D. student in his group, Carolyn Kelly, were able to characterize this mutation, uncovering the molecular mechanism of how it altered wild-type ATL function. They also have been working to uncover the broader picture of ATL’s role in the cell. A second study was focused on understanding how ATL’s activity is regulated in the cell. In the course of this investigation, Dr. Sondermann’s team identified several new modes of regulating ATL’s activity, including a mechanism in which ATL may interact with a number of other cellular components. Further study of these interactions will continue progress to link ATL’s known function with its disease pathogenesis in HSP patients.
Thanks to You!! Dr. Li is close to developing a treatment for both HSP and PLS!!

Using Patient-Specific Neurons to Explore the Treatment of HSP and PLS through Regulating Mitochondria

Xue-Jun Li, Ph.D.
University of Illinois, College of Medicine

One major barrier in studying neurological diseases is the lack of patient-specific nerve cells to mimic the disease process and to test therapeutic agents. Dr. Li’s group uses stem cells derived from patients to address this problem. A breakthrough in the stem cell field is the discovery of induced pluripotent stem cell (iPSC). With the iPSC technology, scientists can convert patients’ skin cells or blood cells into stem cells. These stem cells can be expanded and directed into specific type of nerve cells. This technology provides an unlimited source of nerve cells from patients. In their study, they aim to test the effects of special agents on nerve cells derived from hereditary spastic paraplegia (HSP) patient iPSCs. These agents target mitochondria, the powerhouse of our cells. In particular, they examined nerve cells from SPG48 patient iPSCs and compared with SPG11 iPSC-derived nerve cells. SPG11 and SPG48 are two forms of HSP. They often accompany with symptoms seen in Parkinson’s disease. Their previous work reported the impaired function of mitochondria in SPG48. Mitochondria are important for maintaining normal function of nerve cells. This is because nerve cells have a high energy requirement. However, whether targeting mitochondria can rescue these disease phenotypes in SPG11 and SPG48 is largely unknown.

Using stem cell models of SPG11 and SPG48, the goal of this study is to understand two questions. First, how does mitochondrial dysfunction lead to nerve cell degeneration? Second, what are the protective effects of a

**Figure 1.** A schematic illustration shows the generation of patient-specific nerve cells from induced pluripotent stem cells (iPSCs) that are reprogrammed from patients’ skin cells. Adapted from (Chamberlain SJ, Li XJ and Lalande M. Neurogenetics, 2008, 9: 227-235).
peptide that targets mitochondria? Their data showed impaired mitochondrial dynamics and reduced mitochondrial health in both SPG11 and SPG48 patient iPSC-derived nerve cells. Moreover, mitochondrial dysfunction can impair cytoskeletal organization. The latter is important for the structure and function of nerve cells. Cytoskeletal disorganization is an important defect. The defect needs to be corrected for functional improvement. Using a small peptide that targets mitochondria, they found this peptide rescued the degeneration of patient nerve cells. This small peptide also reduced the impaired cytoskeletal organization and degeneration of SPG11 and SPG48 nerve cells. Taken together, these data suggest that impaired cytoskeleton organization and mitochondrial dysfunction play important roles in the disease progression. Moreover, targeting mitochondria can rescue the degeneration of nerve cells in SPG11 and SPG48. This provides a potential target for treating these HSPs. Given that iPSCs can be generated from different types of HSP, as well as PLS, the strategy and findings in this study will also provide valuable insights into other forms of HSP and PLS.

AT THIS TIME, BIOMARKERS FOR HEREDITARY SPASTIC PARAPLEGIA AND PRIMARY LATERAL SCLEROSIS HAVE NOT BEEN IDENTIFIED.

Biomarker Analysis in Hereditary Spastic Paraplegia and Primary Lateral Sclerosis

John K. Fink, M.D., Professor, Department of Neurology University of Michigan

In general, the term “disease biomarkers” refers to physical, behavioral, radiologic, or molecular features that are 1) associated with a disorder; 2) vary in their degree according to the state of the disorder (either the pathologic processes, the degree of symptoms, or both). To be useful for disease monitoring, biomarkers must be measured serially in clinically available samples (e.g. blood, urine, cerebrospinal fluid, EEG, MRI scans, or electrophysiologic studies such as nerve conduction or spinal cord conduction studies). Identifying biomarkers associated with hereditary spastic paraplegia and primary lateral sclerosis could be used as “outcome parameters” to judge the effects of experimental treatments. Whereas a change in walking ability in response to experimental treatment could take months or years, it is possible that biomarkers could change more quickly, for example over days and weeks. This would allow clinical trials to be conducted more quickly. For example, a number of potential agents could be tried in parallel in a limited number of animal models and human subjects to see if any agent affected the biomarker. In addition to their value as outcome parameters for therapeutic trials, identification of biomarkers may provide insight into pathologic processes (or consequences of these processes) occurring in these disorders.

At this time, biomarkers for hereditary spastic paraplegia and primary lateral sclerosis have not been identified. Their investigation approaches the search for HSP and PLS biomarkers by examining a class of chemicals known as microRNAs. Genes encode proteins by being transcribed into messenger RNA, which is then translated into specific proteins. In contrast to messenger RNAs, microRNAs are not translated into proteins. MicroRNAs serve to regulate genes by affecting gene activity (e.g. the rate of gene transcription into messenger RNA) or by affecting the stability of the messenger RNA itself. For example, microRNAs that reduced the stability of a specific messenger RNA would reduce the abundance of that gene’s encoded protein.

Thanks to you!! Dr. Fink is getting HSP ready for Clinical Trials!!

Continued on page 10
Dr. John Fink chose to investigate microRNAs as potential biomarkers for HSP and PLS because previous studies had shown potential microRNAs, studied in peripheral blood samples, were associated with amyotrophic lateral sclerosis (ALS). Although HSP, PLS, and ALS are separate disorders, all three of these conditions (HSP, PLS, and ALS) share insidiously progressive disturbance of upper motor neurons.

This project has had a number of logistical and administrative delays. For example, subject recruitment was only recently (Feb. 2021) restarted after being paused because of Covid19-related University restrictions for nontherapeutic clinical research. There has also been Covid19-related delays in receiving critical supplies (e.g. an approximately 6 month delay in receiving kits for RNA studies apparently because of a surge in Covid19 [an RNA virus]-related RNA analysis). Furthermore, it has proven logistically challenging to obtain blood samples in the morning (after an overnight fast) and have these samples shipped immediately on dry ice. Samples arriving thawed (despite being shipped with dry ice) can not be analyzed. Presently, samples from 17 subjects are being analyzed in the University of Michigan Center for Advanced Genomics. Samples from an additional 10 to 15 subjects were collected in June, 2021.

Phase 1 (now underway) of this investigation will determine if there are individual microRNAs or combinations of microRNAs present with substantially different abundance in subjects with HSP or PLS compared with healthy control subjects. Phase 2 (Summer, 2021) will be to repeat this analysis in samples collected from a separate set of HSP, PLS, and Control subjects. Candidate microRNAs that show a disease (HSP or PLS)-specific concentration patterns in both data sets will be selected for further analysis. Dr. Fink expects to conclude Phases 1 and 2 within the next 3 to 4 months. Phase 3 (Fall 2021) will analyze messenger RNA patterns (“profiles” that correlate with (i.e. are possibly affected by) changes in microRNAs.

Thanks to you, Dr. Iacoangeli is getting closer to determining the cause of PLS.

**Investigating The Genetic and Environmental Causes of Primary Lateral Sclerosis**

Alfredo Iacoangeli, Ph.D.
Kings College London

Primary lateral sclerosis (PLS) is the rarest form of motor neuron disease (MND), a condition in which the nerve cells controlling movement degenerate and die. The symptoms include progressive weakness and stiffness of the legs, gradually affecting arms and face. It might cause difficulties with speech and swallowing. Although PLS does not typically shorten life dramatically, it greatly decreases the quality of life.

So far, there is no known genetic cause of PLS. Most people with it do not report other affected family members. While PLS mostly develops in midlife, there is a juvenile form (JPLS), which occurs in childhood and young adults. JPLS is caused by mutations in a gene called ALS2. Due to the rarity of PLS, there are no large-scale genetic studies to identify additional genes.

One of the biggest challenges faced by people with PLS is delayed diagnosis and misdiagnosis, since the initial symptoms can be similar to amyotrophic lateral sclerosis (ALS), the most common form of MND. In the absence of a concrete genetic test that differentiates PLS from other MNDs, this delay in diagnosis is inevitable. Understanding the genetic basis of PLS might help in reducing the diagnosis time from the onset of symptoms, and importantly, it is likely to improve our understanding of the condition, ultimately leading to the development of a treatment. As it’s well known that environmental causes such as smoking can irreversibly damage our DNA and cause various health implications, it is also important to investigate these as potential risk factors too.

The main aim of our study is to investigate the genetic and environmental causes of PLS. Through the international Project MinE
Using MRI Techniques to Expedite Diagnosis in PLS and Monitor Disease Progression

Peter Bede, M.D., Ph.D., Associate Professor, Consultant Neurologist, Head of the Computational neuroimaging Group, Trinity College Dublin Medical Patron, Irish Motor Neuron Disease Association (IMNDA) Fellow of the Biomedical Imaging Laboratory, Sorbonne University.

Primary lateral sclerosis (PLS) is a rare motor neuron disorder with a number of unique clinical features. The diagnosis of PLS is challenging and many patients face a protracted diagnostic journey with a multitude of consultations, a series of tests, and considerable diagnostic uncertainty before their diagnosis is ultimately confirmed. The initial presentation of PLS may resemble to other conditions, such as upper motor neuron predominant amyotrophic lateral sclerosis (ALS) or hereditary spastic paraplegia (HSP) which may add to the initial uncertainty. Clinical assessment centers on the ascertainment of disease-associated features such as increased tone in the limbs, spasticity, increased reflexes and making sure that no other signs are detected suggestive of alternative diagnoses. In the diagnostic phase, brain and spinal cord imaging is primarily performed to rule out other conditions which may also present with limb spasticity, such as bulging disks or a variety of brain changes which may mimic PLS-like presentations. In a research setting, magnetic resonance imaging (MRI) can offer a wealth of additional information. MRI scanners are sophisticated imaging tools which provide high-resolution images of the brain without utilizing X-rays. Novel MRI protocols can detect very subtle changes both in the outer layer of the brain, called the ‘gray matter’, as well as in the internal wiring of the brain called the ‘white matter’. These changes would
not typically be seen on regular scans, unless dedicated research protocols are used which compare scans mathematically to control groups instead of mere visual inspection.

In their research study, they have collected high-resolution MRI data in a large cohort of established PLS cases with accompanying clinical information. Their datasets have been thoroughly interrogated and revealed a number of novel findings. They have established that clinical disability correlates very closely with changes in the motor cortex, the brain region that controls voluntary movement. (Figure 1 below). They have also confirmed that focal brain changes in specific brain regions contribute to the preferential involvement of upper or lower limbs and may also drive difficulties with speech and swallow. They have established that not only the main fiber bundle in the brain is affected which connects the motor cortex with the spinal cord, but also the central bundles which connect the two sides of the brain (hemispheres). Their more recent studies have confirmed that ‘deeper’ brain regions called the ‘basal ganglia’ and the ‘thalamus’ are also involved in PLS and are likely to contribute to the variety of presentations. Furthermore, a proportion of patients exhibit widespread cortical changes on the surface of the brain outside the motor cortex. These findings challenge the traditional view of PLS as a pure motor system disorder. Their most recent studies focused on improving the diagnostic process and evaluated patients with a shorter symptom duration of 2-4 years. Interestingly, in this cohort they can already detect brain changes consistent with established PLS.

In summary, they found that computational neuroimaging not only offers invaluable academic insights, but these may soon be developed into pragmatic clinical applications to expedite the diagnosis and monitor brain changes over time. The development and validation of objective markers in PLS is hugely important as these may be utilized in future clinical trials.

Their study is generously sponsored by The Spastic Paraplegia Foundation and they remain committed to communicate their research findings in peer-reviewed scientific journals so that their results are duly shared with the international PLS community. They have also been keen to present their findings at various international meetings to raise awareness of this condition, engage in coordinated research efforts, initiate collaborations and discuss the broader role of neuroimaging in therapy development.

Thanks to you, Dr. Paganoni is discovering a faster way to diagnose PLS.

**Imaging of Neuro-Inflammation in PLS and HSP**

Sabrina Paganoni, M.D., Ph.D.
Massachusetts General Hospital

The Spastic Paraplegia Foundation is funding Sabrina Paganoni, M.D., Ph.D. and her team of researchers at Harvard University, Massachusetts General Hospital (Boston, MA) to find out if neuro-inflammation (a type of inflammation that happens in the brain) happens in PLS and HSP.

*Figure 1. Internal (left) and external (right) brain changes in primary lateral sclerosis detected by dedicated research protocols.*
Why would neuro-inflammation have an impact on the function of the Upper Motor Neurons? Think of the telephone game when you whisper a message and it gets distorted by the time it reaches the last person, and the more outside noise there is, the more the message gets distorted. The brain is trying to send messages to the spine and the Upper Motor Neurons with a system much like telephone cables. If neuro-inflammation causes a lot of outside “noise”, that could reduce the ability of the Upper Motor Neurons to function properly.

The study team has shown that neuro-inflammation plays a role in both PLS and ALS. As shown in figure 1 (above), people with PLS and ALS have much more neuro-inflammation (shown in yellow/red) than expected and this neuro-inflammation is localized to the motor regions. Importantly, the pattern of neuro-inflammation is different in PLS compared to ALS (a different disease that can be initially confused with PLS). Figure 2 (below) shows that the areas of maximum neuro-inflammation are different in PLS compared to ALS, suggesting a possible new way of differentiating between the two.

The team is now completing the evaluation of people with HSP. As shown in Figure 3, results so far suggest that there is no neuro-inflammation in people with SPG7 and SPG4 HSP.

The team is now enrolling a few more participants with PLS and HSP to conclude the study. Results will provide important insights into the causes of PLS, ALS and HSP and will help identify ways to differentiate between these diseases. These results could in turn help to develop new therapeutic strategies.

John Staehle 1946 - 2020
SPF board member, Synapse Newsletter Senior Editor 2013 to 2020, North Texas SPF Ambassador 2005 to 2020.

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Members of The Staehle Legacy League help to assure a future HSP/PLS cure by naming SPF in their will, trust, retirement plan, life insurance policy or annuity.

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The Board of Directors continues to maximize your donations as 92% of each dollar raised supports the foundations’ mission of research, information and support. That 8% that first appears to be overhead is mostly spent on the printing and mailing of our Synapse Newsletter and Annual Report. These publications are mostly geared to informing and supporting our membership with knowledge about how to best manage our lives with these handicaps and updating you on the great progress of our research. Again, our Annual Report expense will be greatly lowered in 2021 by having it available mostly online.

Management and Administration which are valuable and necessary foundation expenses are services which are donated to the foundation. Legal, accounting, income tax preparation, management and medical grant review services are all provided at zero cost but are recorded for tax purposes. We are pleased to report that a total of $771,000 has been approved for research funding for 2020. This is made possible by the continued support of our generous donors. 2020 was highlighted by the Match My Gift program. Over $539,000 was raised as the result of anonymous donor matches. Our heartfelt Thank You goes out to you for your continued support.
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