SPF SPASTIC PARAPLEGIA FOUNDATION, INC.

Research / Education / Support

2014 ANNUAL REPORT

STEPPING FORWARD TODAY TOWARD A CURE TOMORROW

President's Letter

Dear Friends,

Through the generous help of thoughtful supporters like you, 2014 was a giant leap forward for The Spastic Paraplegia Foundation toward a cure for HSP and PLS. You have made it possible for us to be on the forefront of genetic, neurologic and computer science.

During the past year, many new genes for HSP were discovered with over 70 genetic types and 58 identified genes;18 of which have been discovered in just the last 18 months. Gene mutations were even discovered in some subjects with PLS.

You have helped us to develop adult-derived stem cell models to explore disease mechanisms, treatments and models for drug testing. In the past year, disturbances have been discovered in lipid metabolism in some types of HSP and many new animal models have been developed.

What's more, because of you, for the first time, every study that The Spastic Paraplegia Foundation supported in 2014 were for treatments for actual people with HSP or PLS. The preliminary results look very promising.

We are working jointly with the Northeast ALS Consortium (NEALS) to develop methods of better diagnosing PLS early and increasing awareness of PLS and HSP among neurologists nationwide. Together we are creating disease models with animals and people and better understanding how the diseases progress.

The Virginia Freer Sweeney Clinical Research Training Fellowship grant was granted to Christina Fournier, MD. in 2014. Dr. Fournier is studying at Emory University and specializing in the study of PLS. She has already begun several independent studies identifying biomarkers for both HSP and PLS and understanding PLS & HSP Disease Progression by expanding the NEALS Upper Motor Neurological Patient Registry.

Looking forward, this same 2 year fellowship grant is being granted to Sabrina Paganini, MD, PhD to begin in July, 2015. Sabrina will characterize the role of inflammation in PLS using advanced neuroimaging techniques with the goal of developing disease biomarkers and treatments. She will determine the spatial pattern of microglia/monocyte recruitment in the brain in people with PLS and determine the contribution of microglia/monocyte recruitment to PLS severity and disease progression.

Our all-volunteer Board of Directors is diligently working with a large, highly respected, genomics company to open the immense possibility for discovery that whole genome sequencing can provide. We continue working with our distinguished international volunteer Scientific Advisory Board to concentrate and refine our research efforts to make sure every penny of your donation is used in the most opportune way to reach a cure or treatment as soon as possible.

This is an extremely hopeful and exciting time for The Spastic Paraplegia Foundation and it is only possible because of donors like you. Thank you so much!

Sincerely,

Frank Davis

SPF President

CHASING A CURE

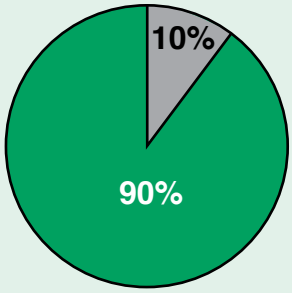
Would you like more information about us?

The Spastic Paraplegia Foundation, Inc. ("SPF") is a Massachusetts not-for-profit corporation that is a nationwide, volunteer-run, health organization dedicated to funding cutting-edge scientific research to discover the causes and cures for Hereditary Spastic Paraplegia and Primary Lateral Sclerosis, and to diminishing suffering by education and support.

The SPF home corporate office is located at 4 Couture Rd., Southampton, MA 01073. A copy of our latest annual report or financial statement may be obtained by writing to the SPF at 4 Couture Rd., Southampton, MA 01073, or calling 877-773-4483.

Financial Activities

Where your dollars go



90% Mission
10% Management and Administration

REVENUE	2014	2013	2012
Donations	$569,276	$443,304	$231,010
Sweeney Fellowship	0	0	338,548
Team*Walk*	44,716	53,436	112,710
Special Events	40,568	59,584	130,269
Program Fees & Products	14,386	12,021	16,795
Investment Income	167	90	143
Total Support and Revenue	**$669,113**	**$568,435**	**$829,475**
DIRECT EXPENSES			
Fundraising	$23,747	$30,736	$50,646
Management and Administration	40,028	41,704	39,408
Program Expense	22,278	28,225	39,040
Total Expenses	**$86,053**	**$100,665**	**$129,094**
GRANTS PLEDGED	**$600,000**	**$800,000**	**$370,000**
FELLOWSHIP	**N/A**	**N/A**	**$200,000**
NET ASSETS	**$1,309,341**	**$1,041,869**	**$1,131,046**

(as of December 31)

The Board of Directors continues to maximize your donations as 90% of each dollar raised supports the foundations mission of research, information and support. In addition, over half of the management and administrative expense consists of web and printed material costs. Other major costs include the annual audit fee, license filings in multiple states and bank credit card fees.

Professional fees which are valuable and necessary foundation expenses are services which are donated to the foundation. Legal, accounting, income tax preparation and medical grant review services are all provided at zero cost.

We are pleased to report that a total of $600,000 has been approved for research funding for 2015. This is made possible by the continued support of our generous donors. 2014 was highlighted by the Match My Gift program. Over $310,000 was raised as the result of anonymous donor matches. Our heartfelt Thank You goes out to them.

Research Review

The Spastic Paraplegia Foundation, since being founded in 2002 has funded over $5,000,000 in research toward the cures of Hereditary Spastic Paraplegia and Primary Lateral Sclerosis. Every year, with your help, we move closer and closer to a cure. Here is just a sample of the progress made in 2014:

Robot Assisted Gait Training Useful for Patients with HSP & PLS

Robot assisted gait training may be useful for providing intensive gait training (with physiotherapy) in patients with HSP and PLS because the patient's walking speed and balance improved after the training.

10 Seo HG, Oh BM, Kim K. PM&R. 2015 Feb;7(2):2103. doi: 10.1016/j.pmrj.2014.09.008. Epub 2014 Sep 22.PMID: 25255290.

Pharmacologic Rescue of Axon Growth Defects in a Human Model of HSP

Skin cells of an SPG3A patient were used to generate pluripotent stem cells, which were differentiated into forebrain neurons. In comparison with control cells, the patient derived cells formed shorter axons, and had alterations in mitochondrial motility. As axonal growth and mitochondrial motility depend on the microtubular cytoskeleton, microtubule stabilizing drugs were tested on the patient derived neuronal cells. These drugs rescued the axon growth defects, indicating that the microtubule cytoskeleton is an attractive target for developing novel drugs in hereditary spastic paraplegia.

Zhu PP, Denton KR, Pierson TM, Li XJ, Blackstone Craig. Hum Mol Genet. 2014 Nov 1;23(21):563848. doi: 10.1093 hmg/ddu280. Epub 2014 Jun 6. PMID: 24908668.

Tubulin Binding Drugs Rescue Peroxisome Trafficking Deficit in Patient Derived Stem Cells in HSP

In nerve cells derived from an SPG4 patient, microtubules appeared to be less stable compared to normal nerve cells. A number of microtubule stabilizing drugs improved the stability and function of microtubules in the patient derived cells. This suggests that microtubule stabilizing drugs may be effective in SPG4 patients. The advantage is here that various microtubule stabilizing drugs have already been tested in humans (for other diseases), and could thus relatively rapidly be evaluated in HSP.

Fan Y, Wali G, Sutharsan R, Bellette B, Crane DI, Sue CM, MackaySim A. Biol Open. 2014 May 23;3(6):494502. doi: 10.1242/bio.20147641. PMID: 24857849 [PubMed].

Hydrotherapy Treatment on Gait Characteristics of HSP Patients

This study demonstrated that Hydrotherapy treatment, for patients with late onset HSP, increased locomotor function and enhanced the patients' ability to perform compensatory strategies, resulting in increased walking speed and step length.

Zhang Y, Roxburgh R, Huang L, Parsons J, Davies TC. Gait Posture. 2014 Apr;39(4):10749. doi: 10.1016/j.gaitpost.2014.01.010. Epub 2014 Jan 29.

PMID: 24556467.

Spastic Paraplegia Proteins Spastizin and Spatacsin Mediate Autophagic Lysosome Reformation

Autophagy allows cells to adapt to changes in their environment by coordinating the degradation and recycling of cellular components and organelles to maintain homeostasis. This study demonstrated that the two most common autosomal recessive HSP gene products, SPG15 protein spastizin and the SPG11 protein spatacsin are pivotal for autophagic lysosome reformation, a pathway that generates new lysosomes.

Chang Jaerak, Lee Seongju, Blackstone Craig. J Clin Invest. 2014 Dec; 124(12); 5249-62. doi: 10.1172/JC177598. Epub 2014 Nov 3. PMID: 25365221

HSP Type 5: A Potentially Treatable Disorder of Cholesterol Metabosim

Spastic paraplegia type 5 (SPG5) is an autosomal, recessive, hereditary spastic paraparesis (HSP) caused by mutations in CYP7B1, which is responsible for a key step in the alternative pathway of bile acid synthesis. SPG5 patients have increased levels of 27-hydroxycholesterol in plasma and cerebrospinal fluid. HMG CoA reductase inhibitors might reduce 27OHC, thus preventing neurological impairment.

Mignarri A, Malandrini A, Del Puppo M, Magni A, Monti L, Ginanneschi F, Tessa A, Santorelli FM, Federicco J Neurol.

2014 Mar; 261(3); 617-9. doi: 10.1007/s00415-014-7253-7. Epub 2014 Feb 8. PMID: 24509641

Stuck in Traffic: An Emerging Theme in Diseases of the Nervous System.

Many mutations in neurological diseases like HSP & PLS affect proteins controlling endosomal/lysosomal transport. Deregulation of endosomal transport is a common theme. This study summarized how elucidating the genetic basis for the various neurological diseases has advanced our understanding of the endo-lysosomal system and why the various mutations all translate into similar disease phenotypes.

Neefjes J, van der Kant R. Trents Neurosci. 2014 Feb; 37(2):66-76. doi: 10.1016/j.tins.2013.11.006. Epub 2014 Jan 8. Review PMID: 244111104

Our most sincere thanks to Dr. Aarnoud Van der Spoel, PhD, Dalhousie Univ., Halifax Canada for his assistance with this information.

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