Deater Foundation, Inc.
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Deater Foundation Newsletter, June 2014

Deater Foundation Helps Sponsor a Third International Symposium: "Molecular Pathogenesis and Therapy of Hereditary Sensory and Autonomic Neuropathy Type 1"

By Tami Newcomer Murphy

The Deater Foundation, Inc. (DFI) recently had the privilege of helping to sponsor a third international HSAN1 symposium, which was held November 14-16, 2013 in Boston. These conferences are a valuable use of DFI's resources as they bring together top scientists from around the world who are working on research to understand the causes, mechanisms, and potential treatments for HSAN1, the disease that has afflicted the Deater family for generations, and has been identified in others around the world.

Researchers presented their work on various aspects of HSAN1, including basic research at the cellular level, animal models, and human trials.

Some of the current research and updates included:

- Dr. Florian Eichler (Massachusetts General Hospital): Presented his findings in HSAN1 mice suggesting that diet may be a factor in how the disease progresses. Feeding the HSAN1 mice a diet high in fat

seems to cause an earlier onset of the disease. Supplementation of the amino acid L-serine in mice has shown that amino acid selection plays a role in the disease, and perhaps lipids (fats) may as well. This may help explain why some people get the symptoms of the disease earlier, or it progresses more rapidly.

- Dr. Thorsten Hornemann (University of Zurich, Switzerland): Presented his research showing that when the disease causes other amino acids (alanine and glycine) besides serine to be used by the mutated enzyme, the byproduct that is formed cannot be broken down and gotten rid of by the body and becomes toxic to nerve cells. These byproducts can be found in the blood and in the nerves. These byproducts have also been found in the blood, but not the nerves, of mice with diabetes, and giving serine to diabetic mice was shown to improve their neuropathy significantly by the end of the study. This might be an indicator of what actually drives the neuropathy and whether or not focusing on just lowering the byproduct in the blood would be sufficient to treat the disease.
- Dr. Dominic Campopiano (School of Chemistry, Edinburgh, Scotland): Presented updates on the structural biology of SPT (the enzyme mutated in patients with HSAN1) and whether or not drug therapies targeting components of the SPT enzyme itself or the sphingolipid synthesis pathway as a whole might be viable options to consider for treatment development.
- Dr. Teresa Dunn (Uniformed Services University of the Health Sciences): Presented her research into the small subunits of the SPT enzyme and also provided more insight into how the SPT enzyme works as a whole. Her research indicated that many HSAN1 mutations elevate activity of the SPT enzyme, making it harder for the enzyme to be so selective, which in turn leads to alanine and glycine binding instead of just serine. Binding with these other two amino acids resulting in the toxic byproducts. She suggested that one avenue for potential therapy might include finding a method to lower the activity of SPT in HSAN1 patients, and therefore help maintain the enzyme's selectivity for L-serine.
- Dr. Marc Freeman (University of Massachusetts): Presented his research on new insights into the death of nerve cell axons (the long slender projection of the nerve cell), specifically the identification of an axon death-signaling molecule and a novel fusion protein in both fly and mouse models that, when over-expressed, can actually block the degeneration of axons, if the cell body of the nerve is still intact. Future experiments to see how these findings could impact HSAN1 were discussed, including a potential treatment for HSAN1.

Other neuropathies relative to HSAN1 were discussed, including HSAN3 (Dr. Elisabetta Morini, MGH), Hereditary Spastic Paraplegia (Dr. John Fink, University of Michigan), and spinal muscular atrophy (Dr. Kenneth Fischbeck, NIH), as well as lessons learned from these diseases and how that information could potentially be applied to HSAN1. Dr. Anne Louise Oaklander (MGH) presented her research on painful neuropathies and the role of small nerve fibers in these diseases. She suggested that nerve injuries may be a common cause of bone fracture and that losing innervation to the bone may cause the bone to be more susceptible to fractures (as sometimes seen in patients with HSAN1). She also stated that women tend to have more sensory fibers in skin biopsies initially when compared to men (which might help explain the disease variance sometimes seen among HSAN1 patients of different gender), and also that skin biopsies taken in healthy individuals without HSAN1 show that a change occurs normally in small sensory fibers around age 22 (which could also point to a possible explanation as to why a more obvious symptom onset typically occurs around this time in patients with HSAN1). She explained that small nerve fibers may deteriorate due to lack of oxygen, especially in the toes and fingers, and therefore she suggested improving oxygenation to the extremities (hyperbaric chamber, exercise, smoking cessation, etc.) to help stop this loss of small nerve fibers. She concluded with the recommendation that patients with HSAN1 obtain bone scans frequently, especially of the heel area, in order to help monitor any changes that may be occurring.

Dr. Mary Reilly (University College London) presented lessons learned from previous clinical trials in peripheral neuropathies as well as information about the current HSAN1 patient population in London. She brought up discussion on potentially evaluating children who might be at risk for having HSAN1 in order to better understand what is going on in the early stages. She suggested that HSAN1 nerve degeneration is probably happening around ages 6-7, but there are no symptoms in the child yet. Most likely, by the time symptoms become apparent around age 12 or above, there is probably already about a 30% sensory loss of nerves at this point.

The meeting concluded with a discussion on HSAN1 patient populations in Boston and London, review of information obtained from the follow-up surveys done by Dr. Vera Fridman coupled with the original survey from the Deater Foundation in 2007, and the potential for an HSAN1 fly model (Dr. Vincent Timmerman, University of Antwerp). Many new ideas were generated, including improving clinical outcome measures, setting up an international registry of HSAN1 patients, completing a prospective natural history study, and possible pre-symptomatic study. Everyone present agreed to continue making advancements through collaboration and communication in order to further understand this disease. There was also a unanimous interest in holding more HSAN1 conferences in the future and also seeing if research pertaining to HSAN1 could be integrated into the broader-scale neuropathy symposiums held throughout the year, like the annual International Charcot-Marie-Tooth Consortium and/or Peripheral Neuropathy Meetings.

This 3rd symposium was a productive time of research presentation, idea discussion, and potential therapy proposals by these top researchers in order to further the goal of developing a treatment and cure for patients with HSAN1. We thank you all so much for your donations to DFI, and we want you to know that your generosity helped make this important meeting possible!

(And for those who might be interested, a more detailed scientific explanation of some of the research presented at the conference can be found on our website, www.deaterfoundation.org)

The current research has introduced us to others with HSAN1.

Meet Helen Turner:

Hello, I developed symptoms of Hereditary Sensory and Autonomic Neuropathy Type 1 "due to a T399G missense mutation in serine palmitoyl transferase" when I was 27. I am currently 52. My symptoms started in both feet and my symptoms include numbness, tingling and pain in the feet and hands. I experience motor symptoms such as weakness and loss of muscle particularly in the lower leg and feet muscles. I wear Ankle Foot Orthotics to support the drop foot. Within the past 10 years my hands and fingers have also been affected. I have had partial loss of fingers due to minor injuries where I cannot feel pain and cellulitis that has caused severe damage to my fingers. The slow-healing wounds on my fingers have developed into chronic ulcerations. I have had cellulitis many times and had many surgeries and partial amputations of several fingers.

My mother had HSAN. Her father and his mother also had it. (Helen's family called the disease "Clark's disease", the last name of her great-grandmother). My oldest brother has it; my sister, does not have it. We were all born in England.
Elise A. Johnson (Dr. Eichler's research coordinator) put me in touch with Marsha Wall in Oregon. She is the first person that I have ever spoken to that has this same disease. I have never found out this much information in the past 25 years.

Update on current research

By Florian Eichler, M.D. Massachusetts General Hospital

HSAN1 Trial Update: The two-year, double-blind, placebo-controlled trial studying the efficacy of L-serine in patients with HSAN1 is well underway. Eighteen individuals enrolled to date. Sixteen subjects were enrolled between mid-September and early December. Two more were enrolled in early April. To date, 16 subjects have completed their 6 month follow-up visit. We need two more subjects to reach our target enrollment of 20. No adverse effects have been attributed to L-serine.
The study is randomized to placebo versus study drug, and the investigators are blinded to who is on placebo and who is on study drug. Therefore we cannot at this point report any conclusions. However, we hope that in the second year, data analysis will allow us to report some insights. A full assessment will not be possible until all patients have completed the two year trial.
As HSAN1 is thought to be to a rare disease, we have been surprised at the rapid enrollment. We credit the Deater Foundation greatly for their support and attribute the successful enrollment to date in large part to their effort. It also shows that trials bring about greater disease awareness and patient engagement. We hope this momentum will sustain and help recruit the remaining two patients needed.
Soon to be published study on the Natural History of HSAN1: In a recent collaborative natural history study between MGH and UMass, we found that while standard nerve conduction studies are reliable in assaying large fiber function in HSAN1, they do not adequately measure small fiber function. This is because these small fibers do not contribute to main components of nerve conduction studies. We found that the best objective diagnostic tests for small fibers are distal-leg skin biopsies that assess density of small-fiber skin innervation.
New Center Initiative at MGH: Recently, MGH has become part of the CMT Rare Diseases Clinical Research Network (RDCRN). HSAN1 has the potential for broad impact in the field of hereditary neuropathies. We are glad that through participation in this consortium we will be able to communicate our insights in HSAN1 more effectively. The CMT community has the ability to make patients and physicians more aware of HSAN1.
Natural History in Children of Patients with HSAN1: During the last HSAN1 meeting, many of the investigators were enthusiastic about proceeding with a natural history study in children of patients with HSAN1. At the time the thought was to study all children regardless of whether they carried the mutation or not. This would prevent difficult ethical issues as well as allow for an important control group. However, the IRB application and study documents are still preliminary and have not been finalized. We look forward to a natural history study in children of patients with HSAN1. We will work with Drs. Brown, Oaklander and Fawn Leigh, a pediatric neurologist with neuromuscular expertise at MGH, to accomplish this goal. We are poised to carry out this study, but will need continued support from the Deater Foundation to make this possible.

Lastly, we give many thanks to:
Dr. Oaklander, Dr. Novak, Dr. David, and Dr. Fridman. Thank you for your expert assistance with the trial.
The Deater Foundation. Participation from the family has been extraordinary and contributes greatly to the success of this trial. Elise Johnson (coordinator) states that it has been a pleasure to work with each and every individual in the trial. She thanks them for their dedication and positive support.
The MGH neurogenetics DNA diagnostics laboratory. HSAN1 trial brochures were mailed to all individuals that tested positive for HSAN1. The lab's assistance in recruitment allowed us to discover another individual with HSAN1 who is currently enrolled in the trial.

Meet Marsha Wall:

I have HSAN1 with the C133Y mutation, the same as the Deater family. I started having problems with my feet when I was in my teens. The doctors said that I have some kind of nerve disorder. I was tested in my 20s and told I had a congenital neuropathy. I continued to have more problems with my feet, and then with my hands including cellulites and various infections leading to osteomyelitis.

At 19 I lost my first toe, and then so on. I had a below the knee amputation of my right leg at age 40. I have no feeling in both legs at just above the knees and in my hands and arms at the elbows.

I was tested again and told I had Charcot-Marie-Tooth type 2 (CMT). When I started with a new doctor two years ago he felt that what he was seeing was not CMT, but something different. I had genetic testing done at the MGH neurogenetics lab and was told I have HSAN1. I got information from the lab about the study, and Elise Johnson told me about the Deater Foundation website. For the first time, I saw pictures of hands that looked like mine. Elise put me in touch with Ellen Deater Burns, who lives only 3 miles from me. My family does not have a history of HSAN1 or CMT. My father has been tested and does not have the HSAN1 gene. I am one of six children and the only one with this.

I am now having problems with my eyes and have been diagnosed with Best disease (vitelliform macular degeneration). I also have loss of hearing in my right ear, and I'm only 50. Can't wait to find out what I get in my 60s! But life is good, too.

Enterprise Holdings Foundation Donation

The Enterprise Holdings Foundation has once again awarded The Deater Foundation a generous grant, thanks to an application by Jon Ellsworth, a manager for Enterprise Rent-A-Car in Florida. **The $4,500 given this year is an increase of $500 over the record amount donated last year. Enterprise has provided the Deater Foundation with over $28,000 in the 8 years that the organization has supported our cause.**

The mission and commitment of the Enterprise Holding Foundation states:
The Enterprise Holdings Foundation gives back and strengthens through charitable support the thousands of communities where our employees and their customers work and live.
Our giving flows from the belief that we owe our success to the communities we serve, and we must support their good causes in return.

We encourage others to check with the Human Resources Department at your workplace to see if you company offers a grant or gift matching program to benefit non-profit organizations.

New grant awarded to study small-fiber polyneuropathy

By Anne Louise Oaklander, M.D. Ph.D, Massachusetts General Hospital

The Nerve Injury Unit at Massachusetts General Hospital has been awarded a grant from the Department of Defense to study Gulf War Illness, a currently unexplained chronic illness that affects some veterans of the 1990-1991 Persian Gulf War, causing multiple symptoms including fatigue, chronic widespread pain, memory loss, skin changes, and gastrointestinal disorders. The causes of Gulf War Illness are unknown, but some war fighters might have been exposed to toxins or infectious diseases during their service.

The Mass. General team, headed by Anne Louise Oaklander and Max Klein, will look for evidence that some cases of Gulf War Illness may be caused by underlying small-fiber polyneuropathy. The grant will provide them the resources to work with neuropathy experts from around the world to develop a formal case definition for small-fiber polyneuropathy and to clarify the best ways to diagnose and monitor it.

This work is relevant to HSAN1, a different type of neuropathy, because some HSAN1 symptoms are caused by small-fiber polyneuropathy. At present, there are no widely accepted ways of identifying specific HSAN1 symptoms or testing for them, and the Gulf War grant should help develop these. The Mass. General team particularly focuses on neuropathies that start in childhood and the young adult years, so the tools they develop may be directly applicable to HSAN-1. Unlike most research groups, they have IRB permission to study children, with permission for some tests going down to age 3. The Mass. General group has already been conducting research on the Deater neuropathy in collaboration with Drs. Florian Eichler and Vera Fridman. We look forward to even closer collaboration with them in the future after their new Department of Defense grant starts.

Nerve Injury Unit at Massachusetts General Hospital Team

New Study Proposed for "Creating an *in vitro* model of HSAN1 in which to study disease mechanisms and potential treatments."

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

Our objective is to grow nerve cells (neurons) from individuals with HSAN1 in the laboratory ("in vitro"). We want to examine these neurons for patterns of nerve degeneration, and importantly, use these cultures to screen chemicals to find potential treatments. Our approach is to obtain superficial skin biopsies (3 millimeter diameter) from individuals with HSAN1 (and from normal control subjects), grow skin fibroblasts, and transform these fibroblasts into adult stem cells. We then differentiate these stem cells into neurons and study molecular mechanisms of degeneration and treatment approaches. Once developed, stem cells from HSAN1 subjects will serve as an important resource that can be distributed to other investigators so that studies into mechanisms and treatments for HSAN1 can proceed simultaneously in many laboratories. Our studies are approved by the University of Michigan Institutional Review Board.

Gene silencing studies being conducted at the University of Massachusetts

By Robert H. Brown, Jr., M.D. PhD.

Dr. Brown reports that "Havisha Karnuam is an outstanding MD-PhD student" in his laboratory, who is being co-mentored by Dr. Brown and "an extremely capable, knowledgeable faculty member, Prof. Anastasia Khvorova, who has many years experience (including patenting relevant inventions) in gene silencing". Havisha has generated modified oligonucleotides, which are short single stranded DNA or RNA molecules that can be used as tools to study gene function or as therapeutic agents. Oligonucleotides can inhibit expression and induce a blockade in the transfer of genetic information from DNA to protein, thereby "silencing" the gene. The oligonucleotides Havisha has generated silence the gene for the SPT (serine palmitoyltransferase) enzyme, a mutation of which is responsible for HSAN1, in the laboratory. Her research on the gene causing HSAN1 is Havisha's doctoral work. She has completed one year on this project and will continue this work for about another 3 years. Dr. Brown states that "Dr. Khvorova has been terrific – and has had a pivotal role in Havisha Karnuam's success."

This approach, at the level of the disease causing gene, is an entirely different method to seeking a cure for the disease HSAN1. There is precedence in another hereditary disease, however. Lipoprotein lipase deficiency is a different rare autosomal recessive disorder in which people with the disease are unable to metabolize fat particles carried in their blood. The first gene therapy approved by authorities in the western world was achieved when the European Commission approved gene therapy treatment for this disease last year.

Deater Foundation Inc Treasurer's Report

Nancy Adams Newcomer, Treasurer

Balance as of 6/1/13	$28,253.25

Income:		Expense:	
Contributions 6/1/13 to 12/31/13	$7,383.88	Sept 2013 Mass General Donation	$10,000.00
Interest 6/1/13 to 12/31/13	5.61	Network for Good Service/ PayPal Charges	22.96
Contributions 1/1/14 to 5/31/14	6,980.05		
Interest 1/1/14 to 5/31/14	1.83		
		Balance as of 5/31/14	$32,601.66

Your contributions make the work of the Deater Foundation possible. You may be a family member, a friend or neighbor, or a complete stranger to someone afflicted with the progressive nerve and muscle wasting disease that is HSAN1, or you may be coping with the disease yourself. The research for this disease takes time and money. Most of our researchers are working primarily on other projects with greater funding. We are profoundly grateful for their interest and dedication to this rare disease. They could do so much more with additional support. Thank you for your generous donations of prayer, encouragement, and money. The struggle continues; together, we will find a treatment and a cure.

Reunion Reminder

Hope to see you at the 72nd Deater Reunion on Saturday, July 19th, 2014 at Butler's property!

The Deater Foundation Meeting is held immediately after the family meeting, at about 1:30 pm. All are invited to attend.

DFI

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Your contributions to DFI are tax deductible.

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