



Deater Foundation, Inc.

PO Box 255
White Deer, PA 17887

Deater Foundation Newsletter, June, 2013

President/Secretary:

Carol A. Dorward

Vice President:

Eric Newcomer

Vice President/
Medical Liaison:

Ellen Burns

Vice President of
Development:

Tami Murphy

Treasurer:

Nancy Newcomer

Due to the illness of our President/Secretary and Newsletter Editor for many years, this newsletter is in a letter format. Our thoughts, good wishes, and prayers go out to Carol Dorward for a quick recovery. Eric Newcomer is the acting President.

Research Recap Highlights

It was in 1986 that Dr. Robert Brown came to the Deater family reunion and drew blood from family members to begin a study of Hereditary Sensory and Autonomic Neuropathy Type 1 (HSAN1) at the Day Laboratory for Neuromuscular Research at Massachusetts General Hospital. In 1989, Carol Dorward and Nancy Newcomer conceived of the idea and established The Deater Foundation to support research into HSAN1. By 1992, Dr. Khemissa Bejaoui was involved in the research at the Day Lab. In the March 2001 edition, volume 27, of the prestigious scientific journal *Nature Genetics*, two articles were published that were the culmination of years of research involving the Deater family and other families with HSAN1. Dr. Garth Nicholson and his team in Australia identified a genetic mutation causing the disease in patients in that country, and Dr. Bejaoui independently confirmed the mutations in other patients, including those in the Deater family. Several mis-sense mutations were identified, classified as C133W (the most common), C133Y (in the Deater Family) and V144D.

In 2004 Alexander McCampbell, then at the Day Lab, developed a mouse model for HSAN-1. Genes in mice were altered, resulting in mice with a transmutation gene for the C133W mutation. When Dr. McCampbell left the Day Lab, Dr. Florian Eichler had joined Dr. Brown at the Day Lab, and took over responsibility for the mouse studies.

On April 24, 2008 a Symposium funded by the Deater Foundation was held in Boston and brought together researchers from as far away as Switzerland and Australia to discuss the cause and treatment for HSAN1. A trial of supplemental L-serine to mitigate symptoms of the disease was suggested at this conference. In July 2008 Diane McKenna-Yasak from Dr. Brown's laboratory collected blood samples from family members at the Deater Reunion to research specific bio-markers of the disease.

July 19, 2009 saw the initiation of a 10 week study of the effect of supplemental L-serine on HSAN1 in volunteer members of the Deater family. The study was funded by the Deater Foundation and was conducted by Dr. Brown and Dr. Eichler.



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In early 2010 the Deater Foundation contributed \$10,000 to a newly established Deater Foundation Fund at the University of Massachusetts, Worcester Campus, where the Medical School is located. This money was used to fund a second Symposium on HSAN1 held, in February, in Boston where, among other things, the results of the 10 week study were reviewed. Shortly before this, Dr. Brown had accepted the appointment as Chair of the Department of Neurology at the University of Massachusetts Medical School and UMass Memorial Medical Center because of its emphasis on genetics. Dr. Eichler continued the research, focusing on the HSAN1 mice, at Massachusetts General Hospital (MGH) with his own laboratory there.

Over the course of several years, Natural History studies in the form of a questionnaire and follow-up questions, developed and coordinated by the Deater Foundation, went out to affected family members. These are being analyzed by Dr. Fridman at MGH.

Much work has been done by many dedicated researchers and brave study participants to move forward the investigation into the disease that has caused pain and debility in generations of the Deater family and, as we have discovered, many other people the world over.

John V. Shufflebarger, M.D.

Dr. Shufflebarger is a 52 year old board certified hand surgeon from West Virginia. He is now at the University of Massachusetts Medical Center, where he has treated two people with a known diagnosis of HSAN-1, and he suspects that disease in at least one other patient. He is very interested in the pathology he has seen, and is planning to write an article about the changes in the hands of people with "congenital sensory nerve disorders".

Dr. Shufflebarger has asked for photographs of the hands of people with sensory neuropathy. He wants to illustrate his article with "photos of patients with this problem at different ages and with different degrees of involvement." He states, "this will help with recognition of the disorder at earlier stages and prevent the loss of tissue and function we see now. We can review the best preventative measures as well as diagnostic tools." He also wants to address "surgical indications" for intervention. Some people have already sent pictures to him or to his associate, Marissa Matarrese. Dr. Shufflebarger has expressed interest in coming to the Deater Reunion, but before getting started on the article, Dr. Shufflebarger's team would first need to get Institutional Review Board (IRB) approval from his hospital. This can be a lengthy process to insure that peoples' rights and health are not violated by research. When approved, this study will give the Deater family an opportunity to participate in research that may positively impact the treatment of this debilitating disease.

Please Contribute to the Deater Foundation

Except for the minor expenses of PayPal and our internet presence, all the money that is contributed to the Deater Foundation goes to support research into HSAN1. Even the cost of mailing this newsletter is donated. It has been 80 years since the initial studies were conducted on the Deater family. We feel we are at the brink of significant new knowledge that will lead to a cure. Please help us move this research forward with you donations, and with your prayers.



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Current and Upcoming Research

In the fall of 2011 a small pilot study of L-serine supplementation was undertaken by 5 participants with a diagnosis on HSAN1. The data gathered during this study are still being analyzed by Dr. Brown, Dr. Eichler, and Dr. Anne Louise Oaklander. As with the earlier serine supplementation study, there was a decrease in deoxysphingolipid (dSL) levels in blood, but there is still much to learn about how L-serine works upon nerves. Dr. Oaklander and her technicians are going through a rigorous quantification of the skin nerve fiber data. Skin samples were taken in order to look at and count the number of nerve cells in the skin of affected individuals before and after taking the supplement. Unlike previous studies, this study was not focused on the biochemistry but on neurological outcome. Some participants in the study reported positive results:

- “I pretty much had NO pain in my hands while on it. Before taking it my hands would ache every night, sometimes to the point where I just had to go to bed because I couldn't stand it anymore. I also had less pains in my feet while on the serine. I get shooters usually during the night that keep me up and I didn't get them as often and when I did they were very mild. I also noticed a big difference in my balance and felt more comfortable walking around my house without braces on.”
- “Within just a few weeks of being on the serine, I noticed a significant decrease in the frequency and intensity of the shooting pains in my hands and feet/legs I also noticed a slight return of light touch on the back of my lower legs/ankles, which had been gone for quite a few years prior to the serine. “

Other participants did not experience significant change:

- “I didn't notice much functional improvement while on the serine, but my leg pains seem to have increased considerably since the end of serine trial.”
- One participant reported no change at all

It is possible that the response to the L-serine may depend on the specific gene mutation, or on the degree of impairment the person has when starting the L-serine supplement.

During this same time, much work was underway to seek funding for a more extensive, double blind, randomized study of L-serine supplementation. This will be an especially important and essential study, given the great variation in response to L-serine in the small study.

The larger 2 year study, funded by a grant from the National Institutes of Health (NIH), is still in the planning phase. NIH encouraged the research team to perform pharmacokinetic studies on L-serine and provided support for those studies. Pharmacokinetic studies examine the process by which a drug is absorbed, distributed, metabolized, and eliminated by the body. The researchers have integrated that into the protocol and had Dr. Mary Reilly (in England) and other experts give their opinions on the best way to determine relevant measures of the outcome of the study. There is a concern that the measures that were proposed to evaluate the results may not be sensitive enough to capture the impact of L-serine. The research team is holding weekly meetings at Massachusetts General Hospital to be sure everything is in order prior to beginning the study. The protocols have been submitted to both the Food and Drug Administration and the local Institutional Review Board (IRB). Enrollment of study participants is now expected to begin sometime in July, 2013, depending on the response from the IRB.



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Other Research News

Dr. Eichler continues with the mouse studies and reports some significant developments related to diet and other areas of those studies.

A possible connection between the nerve damage occurring in HSAN1 and that found in diabetes is of great interest and researchers are looking into this.

New genetic mutations have been identified that are associated with an even more severe form of HSAN1. This was documented in a May 2013 article in the American Academy of Neurology in which the joint senior authors are Thorsten Hornemann, PhD, and Mary Reilly, MD, FRCP. Both of these researchers have collaborated with Dr. Brown and Dr. Eichler.

Dr. Vera Fridman recently returned from training in inherited neuropathy in London and has completed a paper on the disease progression and biomarkers in HSAN1. The paper is being submitted for publication.

Dr. Brown is working with a MD-PhD student at UMass who has elected to make HSAN1 the topic of her research. She has made important initial progress towards generating a mouse model of the Deater (C133Y) neuropathy in which the mouse gene will be mutated rather than adding a transgene. The goal is to use recent innovative technologies to study ways to silence the mutated gene.

It is exciting and encouraging that research is ongoing and continues to benefit from advancing technologies. Although the process often seems slow and laborious for those of us waiting for answers and solutions, we trust in the future, and are thankful for the present.

Deater Foundation Receives \$4,000 Grant from Enterprise

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 mission and commitment of the Foundation states in part:

- We believe it is important to provide financial resources to worthwhile nonprofit initiatives that are actively supported by our employees, their spouses, and loyal customers.*
- We strive to provide more sizable special grants to nonprofit groups or causes of significant strategic or social importance to our company and our employees.*
- 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.*

The \$4,000 given this year is the highest amount that The Enterprise Holdings Foundation has provided the Deater Foundation in a single year. In the 7 years that the organization has supported our cause, Enterprise has donated approximately \$20,000.

Many companies have a fund or a foundation set up for philanthropic purposes. We encourage you to check with your Human Resources Department to see if your company offers a grant or gift matching program to benefit non-profit organizations.



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Plans for a 3rd HSAN1 conference sponsored by the Deater Foundation

The Deater Foundation has sponsored 2 HSAN1 international workshops, in 2008 and in 2010. The first set the research community on the path to investigate the possibility that the gene defect in HSAN1 involved the creation of a substance toxic to nerves. The second conference proposed that supplementation of L-serine might have positive results on the symptoms of the disease.

These conferences are extremely valuable in bringing together researchers from around the world who are each experts in their fields. Dr. Brown proposed last fall that another conference within the year would be a valuable platform to move HSAN1 research forward. This year's conference will take place in the Boston area November 14-16. Invitations have been extended to "**The Molecular Pathogenesis and Therapy of HSAN1**". As of June 2, 2013, the following plan to attend: Dr. Kurt Fischbeck, National Institutes of Health; Dr. Garth Nicholson, University of Sydney, Australia; Dr. Marc Freeman, UMass Medical School; Dr. Mary Reilly, National Hospital for Neurology, London; Dr. Vincent Timmerman, University of Antwerp, Belgium; and Dr. Anne Louise Oaklander, MGH. These researchers will bring an immense and varied amount of expertise to share.

Advances in biochemistry and genetics have opened potential new avenues of research regarding the HSAN1-associated mutations in the SPT gene. Dr. Brown reports, "two important facilities at UMMS provide an almost unique set of resources for dealing with dominantly acting disease genes. One of these is the set of laboratories that have expertise in using small, inhibitory RNA to shut off genes. Another key resource is the Gene Therapy Center where novel viruses have been discovered that facilitate delivery to the nervous system." RNA, or ribonucleic acid, performs multiple vital roles in the coding, decoding, regulation, and expression of genes. New therapies offer the potential to turn off in the body the mutant gene that causes HSAN1 and to try this therapy in the HSAN1 mice, using specific viruses to move the RNA into the nervous system. This would be an entirely new approach to research in this disease.

The conference participants will review the progress made to date with the mouse studies and the human clinical trial and then will engage with the many still unanswered questions about the disease:

- When does the disease start, and when should treatment start?
- What do we know about the natural history of the disease?
- Are there modifiers such as diet or other genes?
- What is the relationship of HSAN1 to other neuropathies?
- What other therapeutic modalities may be possible?
- Can symptom management be improved?
- How can clinical assessment be done more accurately and quickly?

The Deater Foundation has limited resources. The Foundation Board has approved the allocation of **\$10,000** of the contributions on hand to fund the fall workshop, in the effort to further research into the cause and cure for HSAN1. Your contributions to the Deater Foundation are what make these steps forward possible. Thank you for your continued support of your family and friends.



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Deater Foundation, Inc Treasurer's Report

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Balance as of 6/1/12 \$37,411.02

Income:

Contributions 6/1/12 to 12/31/12 6,413.10

Interest 6/1/12 to 12/31/12 9.73

Contributions 1/1/13 to 5/31/13 4,425.00

Interest 1/1/13 to 5/31/13 2.26

Expense:

Aug 2012 Mass General Donation - 20,000.00

Network for Good/PayPal Service Charges - 7.86

Balance as of 5/31/13 \$28,253.25