HSAN1 Meeting Report

February 18-19, 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 the meeting on Hereditary Sensory and Autonomic Neuropathy-Type 1 (HSAN1) held in February in Boston.

The evening prior to the meeting the participants gathered at the Sonesta Hotel for dinner and conversation. Dr. Florian Eichler had recently returned from the Gordon Research Conference on Sphingolipids held this year in Ventura, California. He reported that during the conference there were at least 3 presentations on HSAN1 and at least 4 poster presentations. Dr. Eichler had the opportunity to meet Dr. Walter Holleran, a pharmacist from the VA Hospital in San Francisco, who is known to the Deater family from skin sample testing he conducted on many family members, along with Dr. Fluhr, a dermatologist from Germany, several years ago. Dr. Eichler said Dr. Holleran continues to be interested in the Deater family and he will contact Dr. Holleran again.

Larry Deater and Rory Robb, Erik and Cindy Newcomer, and Ellen Deater Burns attended the dinner, where the conversation was lively with discussions of cellular biology and physical symptoms of the disease. The interaction continued in hallways and the lounge past midnight as researchers who communicate mainly by e-mail took the opportunity to share ideas and explore new perspectives on HSAN1. This interaction may have been some of the most valuable of the conference!

The next morning the group was transported to the familiar surroundings of Massachusetts General Hospital's research facility in Charlestown, Massachusetts where Dr. Eichler has his laboratory. The agenda for the day was ambitious and presentations soon exceeded the allotted time with questions and dialog.

Robert H. Brown, Jr., DPhil, MD, who has worked with the family for more than 20 years, introduced the history of the Deater Family and the identification of the gene for HSAN1. Dr. Brown is the Chair of Neurology and a professor at the University of Massachusetts Medical School. He reminded us that the main signature of the disease is a small fiber neuropathy. The genetic basis for HSAN1 is a mutation in the gene that encodes a part of the enzyme serine palmitoyltransferase (SPT). The connection between the enzyme and the destruction of nerve fibers is the subject of research from a variety of viewpoints represented at the conference where basic scientists, clinicians, and family members sat side by side.

Florian Eichler, MD, at Massachusetts General Hospital, who attended the Deater Family Reunion in 2009, reported on his work with the mouse model of HSAN1 and the human clinical trial of serine supplementation. His conclusion is that the disease involves a dysfunctional utilization of the amino acid serine. When the mice are fed a diet high in aniline, another amino acid, they develop the symptoms of HSAN1 at a young age. When the mice are fed a diet high in serine, the symptoms are minimized and in some cases have disappeared. Neurons, or nerve cells, do not produce serine on their own. Serine must be available and transported into the body of the nerve cells. During the clinical trial family members with HSAN1 took supplemental serine in doses of either 200mg/Kg or 400 mg/Kg. The levels of certain types of lipids called deoxyspinghoid bases (DSB) that are known to be markers of HSAN1 decreased significantly with high dose supplementation. After the conclusion of the study, the levels of the DSBs returned to the pre testing levels.

The question was asked, “What is wrong with SPT in HSAN1?” and the next researchers proposed theories to answer that query.

Thorsten Hornemann, PhD from the University of Zurich in Switzerland, provided an update on the deoxyspinghoid bases in HSAN1. He has been working closely with Dr. Eichler in analyzing the results of the clinical trial. He noted that deoxysphingolipid levels are elevated in plasma and peripheral nerve tissue, that they are the plasma markers for HSAN1, and that in the laboratory in culture medium, deoxysphingolipids are toxic to nerves.

Hyujung Park, PhD, of Boston University spoke on SPT kinetics. This is the study of how different conditions can influence the speed of chemical processes. This information can lead to a better understanding of the mechanism of the chemical reaction. The SPT enzyme reacts differently to different circumstances.

Annelies Rotthier, PhD, at the University of Antwerp, Belgium, presented a broader look at inherited peripheral neuropathies, including Charcot-Marie-Tooth and the variants of Hereditary Sensory Neuropathy. She introduced a new mutation suspected to be HSAN1. The other meeting participants, however, discounted this single case as unlikely to be a true HSAN1.

Teresa Dunn, PhD, Uniformed Services University of the Health Science, Washington DC, has been working with Dr. Brown and Dr. Eichler for several years. She works primarily with yeast and looks at functions within the cell. Her work investigates the SPT processes at a cellular level.

Jonathan Lowther, PhD works with Dominic Campopiano at the School of Chemistry, University of Edinburgh, Scotland. They combine chemistry, microbiology and immunology to study proteins and enzymes and ascertain the structural characteristics and mechanisms of encoded proteins. By visualizing the structural model, other scientists can better understand how the protein can interact with other elements within the cell.

Peter Novak, MD, PhD at the University of Massachusetts Medical School explained the process of autonomic testing in neuropathies. Tests include several small punch skin biopsies to visual sensory and autonomic peripheral nerves in the skin, a test of sweat production, a tilt table test, and measurement of the heart rate with various tests. Dr. Novak showed actual test results from the first participant in what is planned to be a new study of HSAN1.

Ann Louise Oaklander, MD, PhD at Massachusetts General Hospital said the Deater family changed her perception of HSAN1. She explained that small nerve fibers do not just sense pain but prevent and respond to injury. The nerves involved in HSAN1 can most easily be measured by viewing a skin punch biopsy, as the epidermis of the skin contains the small nerve fibers. From a clinician's viewpoint, Dr. Oaklander talked about neuropathic pain which she says is caused by the remaining neurons firing inappropriately, and about the loss of enervation leading to loss in bone regulation, thinning of the skin and blister formation, and deactivation of sweat glands.

Nazem Atassi, MD at Massachusetts General Hospital spoke about a consortia and trial for rare diseases. This model is in place for the study of Amyotrophic Lateral Sclerosis (Lou Gehrig's disease) with 92 sites of expertly trained clinicians. In this situation Massachusetts General Hospital serves as the coordinator and the State University of New York is responsible for monitoring and outcomes.

Garth Nicholson, PhD from the Concord Clinical School, The University of Sydney, Australia spoke briefly to assert that HSAN1 should be classified as a Charcot-Marie-Tooth disease. HSAN1 clearly has elements of both sensory and motor disorder, and all nerves have autonomic fibers, so the "autonomic" part of the current designation is misleading.

In addition to the presenter there were numerous other participants. Alex McCampbell, who developed the HSAN1 mice and now works for Merck was an active contributor, as were PhD students and people in post doctoral programs bringing fresh perspectives to the conversation.

In the discussion following the presentations the essential question was, "What's next." Dr. Robert H. Brown, Jr. pointed to the initiation of a longitudinal study (mentioned above in Dr. Novak's presentation). This study could start small with the autonomic battery of tests, neurological examination, and background information (a "natural history" of the disease). Various time frames were proposed, from 12 weeks to one year or longer. This could be the core for a larger study that could be conducted at various sites using the same protocol for the families already being studied in England, Australia, and the US. Dr. Eichler is the most likely person to write the protocol for the study. Dr. Brown talked of presenting results as soon as possible at a neurology conference and possible sources of grant funding were discussed.

Larry Deater and Eric Newcomer urged the scientists and clinicians to act quickly. Eric reminded them that, "Every day that you delay, I get worse." We all left with a renewed sense of commitment and hope that new discoveries are on the horizon.