VOLUME 47, NUMBER 3

FALL 2019

National Ataxia Foundation

GENERATIONS

THE OFFICIAL PUBLICATION OF THE NATIONAL ATAXIA FOUNDATION

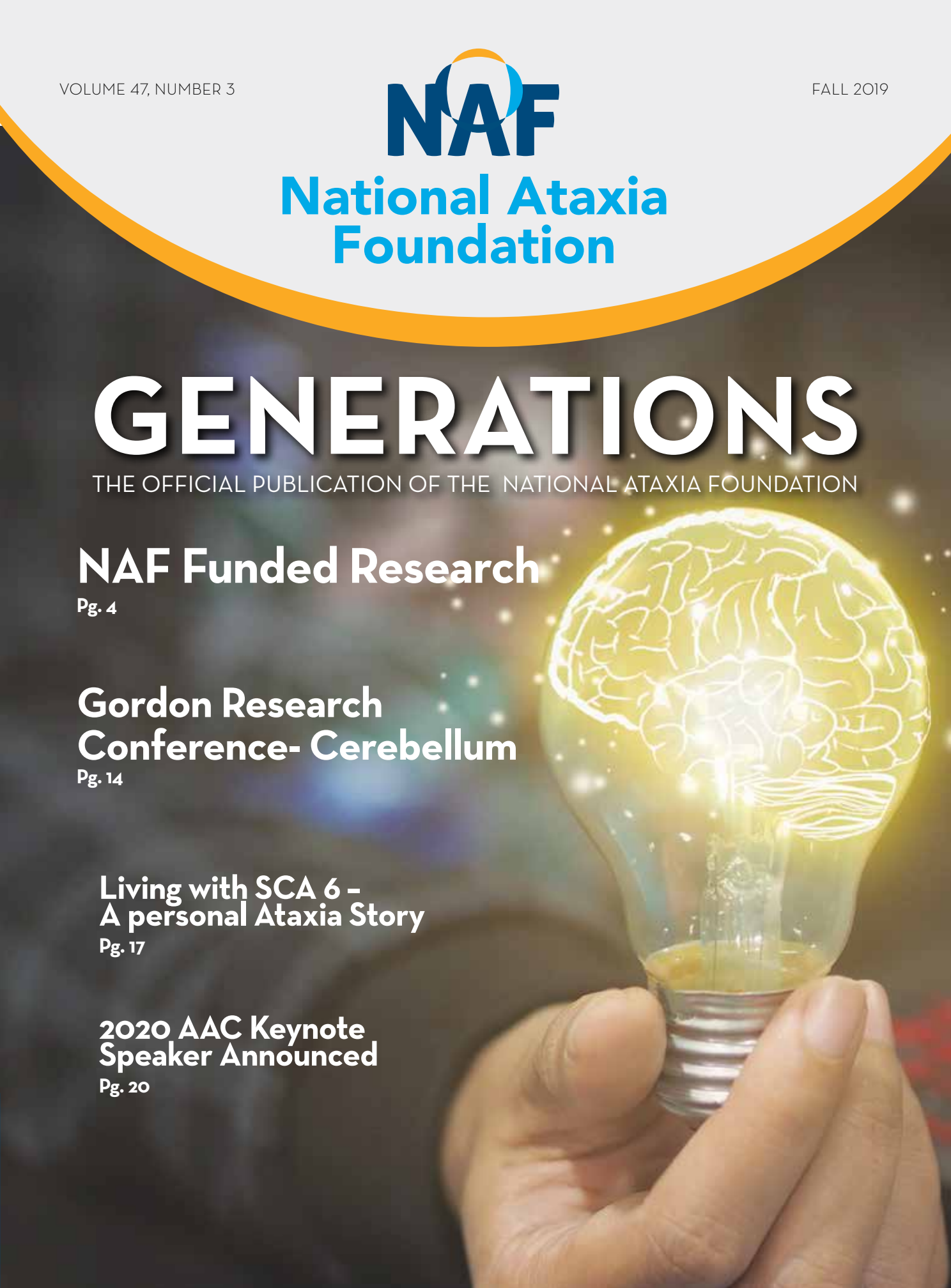


Table of Contents

Deadline to submit materials for the Winter issue of *Generations* is November 4, 2019

Please direct correspondence to:

National Ataxia Foundation
Connecting Ataxia families, researchers, clinicians and the community

National Ataxia Foundation
600 Hwy 169 S., Ste. 1725
Minneapolis, MN 55426
Phone: (763) 553-0020
Fax: (763) 553-0167
Website: *www.ataxia.org*
E-mail: *naf@ataxia.org*
CFC #10752

Generations Schedule:

Issue	Spring	Summer	Fall	Winter
Mail Date	April	July	October	January

Generations Staff:

Andrew Rosen, Executive Director
Sue Hagen, Patient and Research Services Director
Stephanie Lucas, Communications Manager
Mollie Utting, Communications Coordinator
Nick Gullickson, Finance Associate
Leader Printing – Printing and Production
Jessica Johannes – Design

NAF Update:
Letter from the Executive Director

Andrew Rosen, Executive Director

The life of an Executive Director at a nonprofit like NAF is filled with many different tasks. While I enjoy coming to the office and working directly with our talented staff, I treasure the chances I have to get out on the road, meeting with our families, researchers, and pharmaceutical partners as we work toward finding treatments for Ataxia. Let me give you a brief look at a week in September:

Saturday – I attended the 10th annual Minnesota Walk N' Roll to Cure Ataxia. As you know, our Walk N' Rolls take place around the country to help raise critical funds for our programs here at NAF. The Sweeney family started this event and is still very involved with organizing it, along with the help of countless volunteers. It's still going strong 10 years in...no easy task for an event that takes extensive planning. It alone has raised well over $500,000 since its beginning. I was honored to represent NAF and enjoy a beautiful morning with our local Ataxia community.

Monday & Tuesday – What a thrill it was to hear from the leading Ataxia researchers in the country at the Katie Campbell Clinical Trial Readiness Conference. NAF hosted the conference at the University of Minnesota. This annual meeting allows our primary investigators and coordinators from clinical sites around the country to meet in person and share best practices and discuss how to grow participation in the natural history study that NAF helps administer. A number of pharmaceutical companies were also represented, and I can tell you there was a lot of buzz about forming a partnership between clinicians, pharmaceuticals, and the National Ataxia Foundation to accelerate the development of drugs to treat Ataxia. Some of that buzz was just the brain power in the room!

Wednesday – I flew to San Diego and had the pleasure of meeting first with Earl McLaughlin, a former NAF board member. While Earl is living with significant symptoms of Ataxia now, his spirit and unwavering commitment to the Ataxia community is as strong as ever. Earl started the very first Walk N' Roll in San Diego in 2007 in memory of his brother, Charley. I then visited with Jane and Larry Jaffe (after a quick visit to my in-laws, who happen to live a few blocks away!). Jane has led her Tea Time for Ataxia fundraiser for many years. Jane and Larry's support of their daughter, Lisa, is inspiring, and their continued work for NAF is so appreciated. I made a final stop at a pharmaceutical company who is working in the rare disease space and wants to stay connected with the latest in Ataxia happenings.

Thursday – I drove up to Los Angeles, and visited with Drs. Susan Perlman and Brent Fogel at UCLA. Susan is a board member and Medical Director of NAF, and she and Brent serve on our Medical Research Advisory Board. It was wonderful catching up with them and getting their thoughts on how NAF can best work with the pharmaceutical industry as the interest in developing drugs to treat Ataxia continues to grow. But oh... that L.A. traffic! I then fought my way to Orange County to wrap up my week.

Saturday – What a privilege it was to speak at the Orange County Walk N' Roll! NAF board member Cindy DeMint and her family have been running this event for 10 years now, and have built a true community gathering in support of NAF. Cindy and her husband, Gerry, have three sons with Ataxia, and as I said to the huge crowd on hand, they live life every day with grace, determination and humor. They are a true inspiration and a perfect example of why I am so lucky to do the work I do.

There you have it – a week in the life of the ED of NAF. I'm back on the road next week for our "Day on the Hill" in Washington, D.C., in support of International Ataxia Awareness Day on September 25th. I hope to meet many of you "on the road" soon!

Andrew

REMEMBERING NAF IN YOUR WILL

Throughout the years, individuals have named the National Ataxia Foundation as a beneficiary in their wills. Their thoughtfulness and foresight has enabled NAF to provide more research studies, more services to patients and families and more education and Ataxia awareness to the public. We are grateful for the impact that has been made by these compassionate acts. If this is something you would like to consider, please contact Joel Sutherland at ***joel@ataxia.org*** or call (763) 231-2748.

A Look at NAF Funded Research

Each year thanks to the support of our generous donors, NAF funds worldwide Ataxia research. Researchers submit their grant applications to NAF, which are then put through a rigorous review process by our Medical Research Advisory Board. The highest scored and most promising Ataxia research projects are then funded. All these projects are deeply scientific, and the lay summaries of these projects may be difficult to understand. However, we feel it is important to provide NAF supporters with insight into the projects that are funded. The following are lay summaries directly from the principal investigator for each Ataxia research project funded by NAF for the 2018 fiscal year.

RESEARCH SEED MONEY AWARD

Manuela Lima, PhD
University of the Azores, Portugal

Apoptosis-related genes BCL2, BAX, and TP53 as biomarkers of Machado-Joseph Disease/ Spinocerebellar ataxia type 3 (MJD/SCA3)

Despite undeniable progresses in the knowledge concerning the molecular pathology of Machado-Joseph disease (MJD)/Spinocerebellar ataxia type 3 (SCA3), therapeutic compounds remain to be discovered and validated. Interventional trials face several obstacles, namely those related with the clinical outcome measures in use, which lack sensitivity for slow-progressing diseases such as MJD, and cannot be used in the preclinical stage, a time where molecular alterations are known to be already present. Identification of molecular biomarkers, accessible in a peripheral tissue such as the blood, is therefore of particular importance to allow the fine tracking of disease progression, starting at the preclinical stage. Furthermore, once ameliorating drugs are available, molecular biomarkers could help identifying the molecular onset of disease and aid in the therapeutic strategy, since such drugs are expected to be more efficient if administrated to mutation carriers before overt disease. We have been studying gene expression (a process by which information from a gene is used in the synthesis of a functional gene product) in blood samples from MJD patients and pre-ataxic subjects. We had preliminary data indicating that of two genes (BCL2 and BAX) which are involved in an important genetically regulated form of cell death-apoptosis, were dysregulated in blood from MJD patients and pre-ataxic carriers. To these two genes we added a TP53, yet another important pro-apoptotic gene that interacts directly with the protein mutated in MJD, ataxin-3. The goal of this project was to investigate these three apoptosis-related genes (BCL2, BAX and TP53) as peripheral molecular biomarkers of MJD and to access their expression behaviour in brain tissues of MJD patients. Because drug discovery relies on the translation from animal model studies to patient trials, confirming the similarity of molecular alterations occurring in animal models and patients is of high relevance. We therefore also investigated the pattern of expression of the three apoptotic-related genes in blood and brain samples from YACMJD84.2 transgenic mice, a commonly used mice in such trials. Our results confirm that the levels of the anti-apoptotic gene BCL2 are decreased and that apoptosis is activated in blood of MJD subjects, when compared to controls. Noteworthy, when we analysed longitudinal data, generated when samples from the same individuals were collected several times over a period of time, we observed that levels of two of our target genes, BCL2 and TP53 significantly changed with disease progression. Partially analysed results from the experiments with brain samples of the YACMJD84.2 corroborate the presence of dysregulation. Globally these results indicate that cell survival is altered in MJD, and that the direction of such alteration (increased/ decreased) is distinct in affected and non-affected tissues. From the three genes studied, BCL2 is the most promising candidate biomarker. We now intend to replicate these results in MJD subjects from independent cohorts and in an alternative transgenic mouse model.

Weiyi Mu, ScM, CGC
Johns Hokins University, Baltimore, MD

Disclosure of genetic information within families affected by hereditary ataxia

Many ataxias are inherited in an autosomal dominant pattern, where each child of someone who has ataxia has a 50% risk to inherit the same condition. Anecdotally, in some families there seem to be barriers to disclosing this risk. Not communicating to children and siblings that they are at risk for ataxia in a timely manner can result in strained relationships, unnecessary delays in diagnosis, and lack of family planning options. There are currently no published studies on how families with hereditary ataxia communicate risk information and why barriers may exist.

To study these communications and to identify what the main barriers might be, we identified and interviewed 25 people with a diagnosis of hereditary ataxia about risk disclosure decisions. Two separate researchers analyzed the interview transcripts, and looked for common themes discussed by the interviewees.

Results showed that there are many different factors that people consider when deciding when, what, why (or why not), and how to disclose information about their ataxia diagnosis.

Barriers that led some participants to delay or avoid disclosure included complicated family dynamics, emotional factors such as feelings of guilt or sadness, and lack of understanding about how ataxia is inherited. Some participants found it difficult to find a "right time" to share risk information to relatives. Over a third of participants reported not telling someone in their family to avoid burdening them with the knowledge of their risk to inherit the condition.

The data collected from this study will be important in educating neurologists, genetic counselors, and other healthcare providers on how best to support families with ataxia in communicating risk information, identifying and overcoming barriers to communication, and improving understanding of inheritance.

Catarina M Quinzii, MD
Columbia University Medical Center, New York, NY

Nuclear-mitochondrial pathways of neurodegeneration in cerebellar ataxia

Autosomal recessive cerebellar ataxias are heterogeneous neurodegenerative diseases, characterized by incoordination of movement and unsteadiness, due to cerebellar dysfunction. Muscle deficiency of coenzyme Q10 (CoQ10), a mitochondrial lipid which functions mainly as an electron carrier in the mitochondrial respiratory chain and as antioxidant in cell membranes, has been reported in 13% of patients with autosomal recessive cerebellar ataxia of unknown molecular etiology. Although cerebellum seems to be selectively vulnerable to low levels of CoQ, the mechanisms underlying CoQ10 deficiency in cerebellar ataxia, and the role of CoQ10 deficiency in the pathogenesis or progression of the disease are undefined. However, CoQ10 supplementation seems to improve or slow down the progression of the disease, suggesting a role of CoQ10 deficiency in the pathogenesis of these diseases. We and other groups reported CoQ10 deficiency in muscle and/or fibroblasts of patients carrying mutations in APTX, encoding aprataxin (APTX), cause of the autosomal recessive ataxia-oculomotor-apraxia 1 (AOA1). In order to understand the link between cerebellar ataxia and CoQ10 deficiency, we studied APTX mutant and depleted cells. We found reduced expression of the genes involved in CoQ10 biosynthesis, associated with low levels of the transcription factors nuclear respiratory factors 1 and 2 (NRF1/2). Overexpression of NRF1/2 in APTX depleted cells and pharmacological up-regulation of NRF1/2 in AOA1 patients cells rescued the molecular and biochemical phenotypes. Therefore, we conclude that lack of APTX in vitro causes down-regulation of NRF1/2 and their targets genes, including CoQ10 biosynthetic genes, leading to mitochondrial dysfunction. To characterize the pathogenic significance of this

novel nuclear-mitochondrial crosstalk pathway in cerebellar ataxia, we generated neurons pluripotent stem cells derived from fibroblasts of patients carrying APTX mutations. We observed that neurons carrying APTX mutations show CoQ deficiency and decreased level of the gene encoding the first enzyme of CoQ biosynthesis.

In addition, we collected fibroblasts from patients with cerebellar ataxia and CoQ deficiency due to molecular defects different from APTX mutations, and performed RNA sequencing. Our preliminary data show specific sets of genes that are down-regulated or up-regulated in patients fibroblasts compared to controls. We are currently validating these results with different methods, and looking for pathways shared by CoQ10 deficient fibroblasts, APTX mutant fibroblasts and neurons.

Mitochondrial dysfunction is a common feature in neurodegeneration, and nuclear-mitochondrial crosstalk is critical for the maintenance of mitochondrial health. We identified new regulatory nuclear-mitochondrial pathways never before associated with human diseases. Understanding mechanisms underlying mitochondrial dysfunction in cerebellar ataxia is important for the development of novel therapeutic approaches for this and other neurodegenerative diseases with secondary mitochondrial involvement.

Mustafa Sahin, MD, PhD
Boston Children's Hopsital, Boston, MA

Characterization of the disease phenotypes of Ataxia Telangiectasia patient Purkinje cells in vitro

This project's objective was to investigate a novel molecular mechanism potentially leading to cerebellar degeneration in Ataxia Telangiectasia (A-T). It was based on previous discoveries using patient-derived induced pluripotent stem cells (iPSCs), where we had found that a gene encoding a key synaptic protein had a different chromatin structure and alternative splicing isoforms in A-T patient cells compared to control cells. Here, using a protocol recently established in our lab, we differentiated iPSCs into cerebellar precursors and Purkinje cells and confirmed this molecular phenotype in A-T patient derived cells. In addition, our preliminary data showed that patient derived neurons have different neuronal activities compared to cells from healthy controls. More importantly, we were able to analyze brain tissue from multiple patients and controls and confirmed that there exists different splicing isoforms of the synaptic protein, suggesting different synaptic structure or activity in A-T patients. Overall, we have made significant progress towards completing the proposed aims of our pilot grant. Further research is needed to see if this molecular mechanism is applicable to other forms of ataxia diseases.

Matt Scaglione, PhD
Duke University, Durham, NC

Suppression of Polyglutamine Aggregation by a New Class of Chaperone

One class of the Spinocerebellar ataxias (SCAs) are caused by the presence of an expanded CAG tract in the coding region of specific genes. This CAG expansion results in the expression of a protein with an expanded polyglutamine tract. Proteins with long polyglutamine tracts are prone to aggregate and be toxic to cells, therefore identification of ways to suppress polyglutamine aggregation is important. We have found that unlike other commonly used laboratory model organisms the social amoeba Dictyostelium discoideum is resistant to polyglutamine aggregation and toxicity. To accomplish this, we have found that Dictyostelium discoideum encode a novel type of protein that suppresses polyglutamine aggregation.

The goal of this proposal was to both determine the molecular details of how this novel Dictyostelium discoideum protein stops polyglutamine aggregation and to develop a mouse model to investigate if this protein is protective in mouse models of SCAs. We have successfully identified the key portions of this Dictyostelium discoideum protein that suppress polyglutamine aggregation. We also

demonstrated that removing these regions cause the Dictyostelium discoideum protein to lose activity. Future work will focus on developing mechanisms to mimic this region of the Dictyostelium discoideum protein to determine if mimicking it will have therapeutic benefit in cell culture and mouse models of SCAs. In addition, we have also developed the reagents needed to develop a mouse expressing this protein. We anticipate completing this project in the coming months. This mouse model will be useful for determining when and if introduction of this Dictyostelium discoideum protein may be therapeutic in mouse models of SCAs.

Andreia Teixeira-Castro, PhD
University of Mihno, Braga, Portugal

Modulation of neuronal proteostasis by serotonin: impact on SCA3 pathogenesis

Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease (MJD), is a neurological disorder affecting the specific areas of the brain and the spinal cord of patients. The first symptoms usually start around middle age and include difficulty in walking, due to lack of coordination and balance. Other complications, such as problems with vision, speech, and swallowing may also occur. This is a progressive disease and many patients ultimately need a wheelchair or become bedridden, as there is no treatment currently available. We have previously found that chronic treatment with an antidepressant- that targets the chemical of happiness in the brain, serotonin- very strongly improves SCA3-like symptoms in model organisms of the disease, when the treatment is initiated very early in disease progression. Worms (C. elegans) and mice expressing the mutant human gene and protein display abnormal movement and lack of balance and coordination. Antidepressant treatment reverted these phenotypes and decreased the presence of aggregated ataxin-3. Our next step was to mimic the most frequent clinical situation of symptoms driven diagnosis and treatment initiation. We found that when initiated after the onset of symptoms in mice, antidepressant treatment is still beneficial, although to a lesser extent than when initiated pre-symptomatically. Next, we wanted to understand what the drug is doing in the brain that protects against disease. We found that antidepressant treated cells restore the expression of one serotonin binding molecule in the brain and show increased expression of protective genes that enhance protein homeostasis capacity and reduce the risk of formation of aggregated mutant proteins. We are currently identifying in which neurons this protective mechanisms are activated and studying this augmentation in protein homeostasis aptitude as a therapy for SCA3. This study will help us to decipher a series of events that occur in the brain of SCA3 animals and are prevented when the animals are treated with the drug. A better understanding of those events may help the future development of clinical trials in patients and define novel therapies. Besides being useful for SCA3 patients, this antidepressant therapy is also important for patients suffering from other neurodegenerative disorders.

YOUNG INVESTIGATOR AWARDS

Naiara Aquizu Lopez, PhD
University of Pennsylvania, Philadelphia, PA

Uncovering pathogenic mechanisms of cerebellar atrophy in SNX14 deficiency

Cerebellar ataxias are a heterogeneous group of disorders characterized by imbalance and poor coordination due to impaired function or damage to the cerebellum. The condition is often genetically inherited and affects ~9 per 100,000 individuals. Although more than 100 genes have been implicated so far, disease mechanisms for most of the cerebellar ataxias are still unknown and treatment options unavailable. This highlights the need for further studies that will provide better understanding of disease mechanisms and advance in treatment options.

Spinocerebellar ataxia autosomal recessive 20 (SCAR20), is a particular form of cerebellar ataxia diagnosed early after birth and presenting with progressive shrinking of the cerebellum, intellectual disability and dysmorphic faces. Our recent work identified that mutations in the gene Sorting Nexin 14 (SNX14) are the cause of SCAR20. SNX14 is involved in regulating the function of lysosomes, which are the cellular compartments responsible for the degradation of unwanted materials. SNX14 has also been involved in the regulation of lipids. Both lipid and lysosome dysfunction has previously been associated with cerebellar degenerative diseases. However, it is not well understood how they lead to cerebellar damage.

In order to uncover how SNX14 mutations lead cerebellar ataxia, we generated a mouse model that replicates the clinical manifestations of SCAR20 patients. Our work has identified that cerebellar damage in the mouse model begins after birth and not during the embryonic development, suggesting that the disease in humans may also initiate shortly after birth. The analysis of 1-year-old mice, where the cerebellar degeneration is already severe, did not show lysosomal dysfunction, but we found signs of lipid metabolism errors, that may be more sever at the onset of the cerebellar degeneration (at earlier ages). Therefore, our current work is focused on determining the onset of lipid metabolism errors, that may lead to accumulation of toxic cellular materials and lysosome dysfunction, with consequent loss of cerebellar tissue. Our work is now focused on seeking for cellular materials that may toxically accumulate in SCAR20 cerebellum due to lipid metabolism and lysosome dysfunction.

With this study, we expect to uncover disease mechanisms of SCAR20 and routes to prevent the loss of cerebellar tissue. Moreover, our research will help us better understand the relevance of lipid metabolism and lysosomes for the cerebellum and may reveal targets for the development of treatment options for a broader spectrum of spinocerebellar ataxias.

Vincenzo A. Gennarino, PhD
Columbia University,
New York, NY

Delineating the PUM1 functional network in mice and humans

The molecular genetic revolution of the 1990's brought us tremendous knowledge of the genetic mutations that cause many neurological diseases, including many ataxias. In many cases, the disease-driving protein acquires a mutation that causes it to build up in the cell, either because its takes on an abnormal shape that makes it more likely to clump up or because it resists the cell's normal protein recycling and clearance pathways. Further research revealed that, besides having a mutation, there is another way for a protein to cause havoc in the brain: its expression levels might be too low or too high. For example, patients who have a duplication in the region containing the alpha-synuclein gene develop Parkinson's disease, even though the protein encoded by the two genes is perfectly normal. Similarly, duplication of the amyloid precursor protein locus causes early-onset Alzheimer's disease. In both cases, the protein is so abundant that it overwhelms the cell's clearance mechanisms. In the case of Spinocerebellar Ataxia Type 1 (SCA1), mouse studies had shown that overexpression of normal ataxin-1 caused a mild form of ataxia, and that the problem with the mutant ataxin1 is that too much of it builds up in neurons. These observations led me to ask whether reducing the levels of ataxin1 would be a viable approach to therapy. I began to search for factors that regulate the levels of ataxin1. I discovered that an RNA-binding protein called Pumilio1 (PUM1) regulates ataxin-1 levels, and I showed that if you reduce Pum1 levels in SCA1 mice, ataxin1 levels returns to normal, and the SCA1 mice no longer have ataxia.

I also noticed, however, that mice lacking the Pum1 protein developed problems, too: they develop ataxia, in fact, even earlier than SCA1 mice, and they also develop seizures. This led us to suspect that loss of PUM1 might underlie diseases in humans. We reached out to medical geneticists to search for patients with documented PUM1 mutations, and we identified

20 patients with PUM1 deficiencies: those with deletions or severe missense mutations that eradicate protein function suffer from a neurodevelopmental disorder that causes physical, cognitive, and/or psychosocial delay with seizures and ataxia, whereas patients with a milder mutation develop a late-onset disorder that causes a mild, slowly progressive ataxia. PUM1 is thus a newly identified genetic cause of two ataxia syndromes. Given that PUM1 deficiency causes more than just ataxia, and thus clearly regulates proteins besides ataxin1, my next goal was to understand its "targetome," i.e., all the proteins whose levels it regulates.

Thanks to support from the NAF, I have been able to characterize the Pum1 protein-protein interaction network in the mouse brain. Understanding the roles PUM1 plays in neurons will help us understand whether manipulating PUM1 levels in the brain could help SCA1 patients (or, indeed, patients with other neurodegenerative diseases). As my preliminary data indicate that Pum1 regulates a number of proteins involved in other neurodevelopmental and neurodegenerative conditions, the studies are reaping a considerable return on the NAF's investment.

Maja Petkovic, PhD
University of California San Francisco, San Francisco, CA

Elucidating the mechanism of novel spinocerebellar ataxia gene TMEM16K in endolysosomal maturation

Autosomal recessive spinocerebellar ataxia (SCAR10) is a progressive neurodegenerative disease recently identified to be caused by mutations in TMEM16K, a member of an evolutionary conserved family with unknown function at the onset of this study.

To better understand how mutations in TMEM16K lead to ataxia, we have generated the mouse models of the human disease and observed progressive neuromuscular degeneration, consistent with the human pathology. Our study found that absence of TMEM16K leads to perturbed endolysosomal pathway, which is required for proper sorting and degradation of macromolecules, an increasingly central process in neurodegenerative disease.

We found that TMEM16K is localized to endoplasmic reticulum and forms membrane contact sites with the endosomes, acting as a critical mediator of ER-endosomal interorganelle communication. We further demonstrate that TMEM16K phospholipid scrambling activity is required for proper function of the endolyososomal pathway. While reintroducing wild type TMEM16K rescued cellular defects, human point mutants which cause the neurodegeneration could not rescue, suggesting TMEM16K-containing ER-endosome contact sites represent clinically relevant platforms for regulating endolysosomal pathway.

In conclusion, this study has provided insight into the etiology of spinocerebellar ataxia SCAR10 and illuminated the underlying TMEM16K-mediated interorganelle communication supporting endolysosomal function.

YOUNG INVESTIGATOR-SCA AWARDS

Fadi Issa, PhD
East Carolina University, Greenville, NC

Cellular Mechanisms Underlying Spinocerebellar Ataxia Type 13

Spinocerebellar Ataxia Type-13 SCA-13 is a debilitating disease that leads to the degeneration of the cerebellum. SCA13 is caused by specific mutations of the KCNC3 gene, and depending on the type of mutation a patient carries it can lead to either an infant- or adult-onset form of the disease. The KCNC3 gene codes for a protein that is abundantly found in the cerebellum and spinal cord, specifically in the Purkinje neurons of the cerebellum that play critical role in regulating rhythmic activity and body balance during standing and walking. This protein is the Kv3.3

voltage-gated potassium channel whose function allows the Purkinje neurons to communicate properly with other nerve cells within the cerebellum and other brain regions. Therefore, mutation of the Kv3.3 channel is thought to disrupt the ability of the Purkinje neurons to function properly leading to their eventual death. Unfortunately, little is known of how disruption of the Kv3.3 channel ultimately causes the cerebellum to degenerate

To better understand the function of the Kv3.3 channel, Dr. Issa's lab has been using zebrafish to test how disruption of channel activity causes the cerebellum to malfunction and eventually degenerate. In recent years, zebrafish has emerged as a good laboratory model to study neurodegenerative diseases. In addition to SCA disease, zebrafish is being used to study Alzheimer's and Parkinson's disease because their brain development is structurally organized similarly to that of the human brain. More importantly, the cerebellum of zebrafish serves a similar function in regulating balance and rhythmic activity (walking in humans vs. swimming in fish). In addition, since their skin is transparent during early development, Dr. Issa's lab can monitor both morphological and functional changes within the cerebellum in the living fish during the course of development and how introduction of the mutated Kv3.3 channel into the Purkinje neurons leads to malfunction and degeneration.

Using a genetically engineered zebrafish that allows investigators to examine changes in activity of the Purkinje neurons, Dr. Issa discovered that cerebellar cells that express the infant-onset form of SCA13 display heightened activity compared to healthy Purkinje neurons. Interestingly, the mutated cells appear to develop normally early on, but then suddenly degenerate. Their degeneration correlated with the increase in their heightened activity. The finding was surprising to Dr. Issa's team because it suggests that the infant-onset form of SCA13 is not due to mal-development of the cerebellum; rather, it's neurodegenerative in nature, contrary to their initial thinking. This exciting result points to the possibility that abnormally high levels of activity within the cerebellum due to the mutated form of the Kv3.3 protein may underlie rapid cerebellar atrophy observed in the infant-onset SCA13 disease and may serve as a stepping stone to screen for putative Kv3.3 channel modulators that can gate channel activity during development.

Dr. Issa's research findings raise more questions and open new opportunities. Moving forward, his team is interested to learn why expression of the adult-onset mutation of SCA13 does not lead to degeneration despite the abnormally low levels of activity within the Purkinje neurons. Furthermore, they are testing putative drugs targeting the Kv3.3 channel in an effort to rescue its normal function in neurons that express the infant-onset form of SCA13 and determine whether that is sufficient to delay, slow or even block cerebellar atrophy and rescue normal locomotor behavior. With these new insights, his team is confident that their research is well positioned to make new discoveries and improve our understanding of the mechanisms shared with other types of SCA disease.

Damaris N. Lorenzo, PhD
University of North Carolina, Chapel Hill, NC

Regulation of cerebellar development and connectivity by ß-spectrins: implications for the pathophysiology of spinocerebellar ataxias

This award allowed us to generate and characterize two mouse models engineered to lack the **β**-spectrin protein specifically and independently in Purkinje neurons and in granule neurons in the cerebellum. Our motivation for studying the role of **β**-spectrin in the cerebellum is its potential implication in the development of spinocerebellar ataxia type 5 (SCA5) and spinocerebellar ataxia autosomal recessive 14 (SCAR14) originated from the following preliminary observations. A previously characterized mouse model lacking **β**-spectrin in the entire brain had shown severe atrophy of the cerebellum and ataxia, together with other behavioral abnormalities and generalized neuronal deficits. In addition, **β**I-spectrin, another member of the spectrin protein family abundant in Purkinje neurons and which known

mutations cause SCA5 and SCAR14 in humans, had been shown to be functionally linked to β-spectrin in other types in neurons in the brain, such as the cortex and the hippocampus. Deficits in β-spectrin in those neurons cause structural and developmental problems at the cellular and the brain region levels. Thus, we reasoned that the disease mechanism caused by βI-spectrin in the cerebellum in ataxia might also implicate β-spectrin. SCA5 is a progressive neurodegenerative disorder characterized by cerebellar atrophy and profound Purkinje neuron loss. The cellular mechanism of SCA5 is poorly understood.

Our results show some surprising results. First, contrary to our expectations, loss of β-spectrin in Purkinje neurons in mice did not result in obvious cerebellar defects, or in ataxia in mice up to year of age. Since ataxia can often have a late onset and a slow progression, it is possible that manifestations of cerebellar dysfunction may appear later in life. We will continue to monitor these mice as they age for signs of cerebellar degeneration. Alternatively, even if βI-spectrin and β-spectrin may be functionally connected in Purkinje neurons, it is possible that the specific mechanism causing SCA5 does not involve β-spectrin in these neurons. It is also possible that βI-spectrin and β-spectrin have redundant functions in Purkinje neurons, and βI-spectrin, the most abundant of the two in these neurons, compensates for the loss of β-spectrin, but not the other way around. Another surprising finding in our study was that, unlike the Purkinje neuron-specific mouse model, the mice lacking β-spectrin specifically in cerebellar granule neurons did show cellular and anatomical defects in the cerebellum, and resulting behavioral abnormalities. At the cellular level, loss of β-spectrin did not cause changes in βI-spectrin abundance in granule cells or the cerebellum. However, the granule cell layer, a distinct grouping of these cells, was thinner than in normal mice and continued to degenerate as the mice aged. Interestingly, the molecular layer, which is formed by the dendrites of Purkinje neurons, was also thinner. The abnormal anatomy of the Purkinje neurons layer is likely a secondary defect cause by defects in the granule layers. These two populations of neurons in the cerebellum are physically and functionally interconnected, whereas granule cells constitute the main input of Purkinje neurons. Mice lacking β-spectrin in granule cells show hyperactivity, together with loss of coordination and balance, possibly resulting from the abnormalities in their Purkinje neurons. In addition, these mice experienced sporadic seizures, episodes of behavioral arrest, and loss of adaption to modulate response to a familiar stimulus (loss of "pre-pulse inhibition"), a behavior seen patients with psychiatric disorders, such as bipolar disorder and schizophrenia. We are currently investigating the mechanisms underlying these behavioral abnormalities. The resulting deficits in granule and Purkinje neurons abnormalities caused by loss in β-spectrin granule cells raises the question of whether deficiencies in βI-spectrin in granule cells may be a contributing factor to ataxia in SCA5, in addition to their direct impact in Purkinje neurons. As part of our continuing work, we will also follow up on this question.

Pan Li, Ph.D.
Johns Hopkins University, Baltimore, MD

PolySerine protein toxicity in spinocerebellar ataxia type 12

Spinocerebellar ataxia type 12 (SCA12) is a rare neurodegenerative disease caused by a repetitive CAG sequence in exon 7 of PPP2R2B, a gene encoding regulatory units of the protein phosphatase 2A. Based on our preliminary results, we developed a novel hypothesis that proteins containing repetitive Serine (polySer) tract may be present in SCA12 and contribute to the pathogenesis of SCA12. polySer protein has never been studied in SCA12, or in any other expansion disease, and our hypothesis therefore represents a novel approach to neurodegeneration.

We have previously generated and characterized 8 human SCA12 induced pluripotent stem cell (iPSC) lines from three different SCA12 patient skin fibroblast cell lines, and these iPSC lines will be a powerful tool for SCA12 research. By lentiviral infection, we have forcedly expressed a transcription factor NGN2 in these iPSC lines, leading to differentiation to cortical neurons

with high purity. We have developed one more custom made antibody, a reagent that recognizes and detects polySer protein in SCA12. We have also used genome editing method to change the repetitive CAG sequence in SCA12 iPSC lines in order to test the role of polySer in SCA12. We are now at the final stage of this project, and the data we have collected for this project will be published shortly. To sum up, these genome edited iPSC lines will be useful tools for the study of SCA12 pathogenesis, as well as the development of future therapeutic approaches to cure the disease.

Hayley McLoughlin, PhD
University of Michigan, Ann Arbor, MI

Longitudinal profiling of a Spinocerebellar Ataxia Type 3 mouse model's Molecular Signature and Specific Biomarkers

Spinocerebellar ataxia type 3 (SCA3), the most common dominantly inherited ataxia in the world, is a relentlessly progressive and fatal disease for which currently there is no disease-modifying therapy. The polyglutamine repeat expansion in the ATXN3 gene encodes a toxic mutant ATXN3 protein that, when expressed in the brain, ultimately leads to neurodegeneration. With the goal of preventive therapy, several ongoing studies seek to reduce levels of the SCA3 disease protein, including our recent study that showed therapeutic rescue of SCA3 mouse model disease phenotypes after antisense oligonucleotide treatment. A necessary next step toward therapeutic success is a thorough assessment of SCA3 molecular changes over time, so that we can better understand potential neuroprotective pathways and identify promising biomarkers of disease. The focus of this Young Investigator SCA award was to longitudinally profile the SCA3 mouse model gene expression changes that drive disease progression in SCA3-affected brain regions. We rationalized that longitudinal assessment of SCA3 mouse model disease progression may provide opportunity to define early- and late-stage disease mechanisms and also define specific biomarkers across the disease time course. By comparing diseased mouse data to wildtype littermate data over time, we uncovered many changes in gene expression that are closely associated with, and possibly causally linked to, disease progression. To validate these progressive changes and define novel disease biomarkers, we also profiled the transcriptional changes in anti-ATXN3 antisense oligonucleotide-treated analogous brain regions at the mid-stage disease timepoint. This global gene profiling over time, the first to be completed in this model, helped identify many molecular events underlying disease. Ongoing studies in the lab are validating these progressive changes, elucidating possible pathogenic mechanisms, and evaluating candidate genes as promising biomarkers of disease.

PIONEER TRANSLATIONAL SCA AWARD

Maria do Carmo Pereira da Costa, PhD
University of Michigan, Ann Arbor, MI

Exploring the therapeutic capacity of Aripiprazole and related compounds for Machado-Joseph disease

Disease-modifying therapies are lacking for fatal Machado-Joseph disease (MJD), also known as Spinocerebellar ataxia type 3 (SCA3). Our long-term goal is to identify small molecules that are effective to reduce the abundance of toxic ATXN3 protein in brains of MJD patients/carriers and hopefully alleviate disease progression. This project aimed 1) to evaluate the potential of aripiprazole to be repurposed for MJD by carrying out a chronic pre-clinical trial of this drug in MJD transgenic mice, and 2) to develop novel therapeutic compounds structurally related with aripiprazole for this disease that are effective to decrease levels of mutant ATXN3 in neurons. While the preclinical trials are still ongoing, we have preliminary indication that chronic treatment with aripiprazole mitigates motor dysfunction displayed by two MJD mouse models. We are currently evaluating if this improvement in motor performance is accompanied by decreased levels of mutant ATXN3 in brains

of these mice. To develop novel therapeutic compounds for MJD, we carried out structure activity relationship studies building on the chemical structure of aripiprazole. We tested the efficacy of 36 commercially available aripiprazole related molecules and 6 novel compounds generated by us to reduce levels of ATXN3 in a MJD cell line and in human embryonic stem cell (hESC)-derived neuronal progenitor cells (NPCs) harboring the MJD mutation. Two novel molecules show increased potency in reducing levels of ATXN3 in MJD NPCs comparing with aripiprazole. We will further modify the structure of these two novel compounds to improve even further their capacity to decrease ATXN3 abundance in neuronal cells. By tackling two different stages of drug discovery for MJD, we expect to provide proof-of-concept for a fast route for therapy by repurposing aripiprazole for MJD patients and to develop novel compounds of increased therapeutic potential for this disease.

Beverly Davidson
The Children's Hospital of Philadelphia, Philadelphia, PA

Combinatorial Gene Therapy for Spinocerebellar ataxia type 1

There are currently no therapies that delay onset or progression of spinocerebellar ataxia. In earlier work, we showed that gene silencing approaches or gene over-expression approaches delivered individually had a profound positive impact on disease readouts in two animals models of spinocerebellar ataxia type 1 (SCA1). Additionally, our gene silencing therapies in SCA1 mice reversed behavioral deficits and neuropathology, even when delivered after onset. These data are the foundation for future clinical application of gene silencing studies in SCA1 patients. Here, we proposed to expand and improve on this work by testing a combinatorial approach. The goal of this newer approach was to reduce the overall dose of material needed to achieve therapeutic benefit. Results: We were successful in generating new therapeutic vectors. One construct was used to test over-expression of the protective gene ataxin-1-like at multiple doses, the other combined the previously evaluated microRNA, miS1, with the protective ataxin-1-like. The combination therapeutic vector was able to reverse or stop further deficits in gait coordination in SCA1 mice at doses much lower doses that using miS1 alone (two orders of magnitude lower). None of the SCA1 mice treated had any adverse effects.

POST-DOCTORAL FELLOWSHIP AWARD

Alejandro Martin Trujillo, PhD
Icahn School of Medicine at Mount Sinai
New York City, NY

Identification of novel pathogenic tandem repeat expansions in spinocerebellar ataxia

Many types of spinocerebellar ataxia (SCA) are caused by expansions of tandem repeats (TR), i.e, segments of DNA where multiple copies of a sequence are adjacent to each other (CAG-CAG-CAG-CAG-CAG). The ultimate goal of our project was to identify novel pathogenic TRs in unexplained spinocerebellar ataxia (SCA) from genome sequencing data. By utilizing STRetch, a recently released software that allows to detect large TR expansions in sequencing data, we were able to search for repeat expansions across the coding region of the genome in more than 34,000 samples, including ~2,500 with late-onset neurological diseases (307 individuals with a diagnosis of ataxia, 2,154 with Parkinson's disease (PD), and 191 with Alzheimer's disease). In this screening, in addition to identifying many individuals who carry putative expansions of known pathogenic coding repeats, such as those that underlie Huntington's disease and several types of SCA, we identified several novel CAG repeat expansions in brain-expressed genes that were more common in patients with neurological disease. Importantly, one of these regions has been already confirmed by other techniques in the lab and there are several genetic evidences supporting his causative role in SCA. Furthermore, we are currently performing a second screening in 11 unsolved familial SCA cases using long-read whole genome sequencing data. These data will allow us to screen for novel repeat expansions across the entire genome and identify expanded TRs that are likely to be missed by previous sequencing methods.

2019 Research Drive

NOVEMBER 1 — DECEMBER 31, 2019

Support Research today, move us closer to a treatment for tomorrow!

Visit the website to make your donation starting November 1st!

GORDON RESEARCH CONFERENCE — CEREBELLUM

Meeting Co-Chairs: Dr. Megan Carey (Portugal), Dr. Javier Medina (Houston)
Meeting Vice-Chairs: Dr. Daniela Popa (France), Dr. Roy Sillitoe (Houston)

The theme of the Cerebellum GRC 2019 was ***Cerebellar Mechanisms for Movement, Learning and Cognition in Health and Disease***, target areas that are driving how to think about brain function. There were 200 attendees, of which 43 were speakers. The Keynote talk was delivered by Huda Y. Zoghbi (Baylor College of Medicine), who initiated the program and set the stage for a stimulating meeting. Dr. Zoghbi spoke about the mechanisms of Spinocerebellar Ataxia in mouse and human, outlining the experiments that her team, along with the group of Dr. Harry Orr (University of Minnesota), have carried out over the past three decades. Based on this work, she outlined the challenges that pharmacological drugs face in the fight against Ataxia and motor disease in general, but she also provided evidence that alternate therapies such as deep brain stimulation (DBS) remain promising. However, because the cerebellum is now thought to control not only motor functions such as a balance and coordination, but also non-motor functions such as language and cognition, a major portion of the meeting discussed how as single brain region is able to accomplish such a diverse repertoire of functions. Indeed, this is critical for diseases such as ataxia, given that many patients suffer from both motor and non-motor problems. In this regard, the meeting highlighted an impressive series of talks given by junior and senior researchers sharing how they are beginning to uncover what the cerebellum does, and how it does it. Animal models and human research were presented. Based on these discussions, the scientific agenda of the meeting accomplished three goals: 1) A better understanding of the mechanisms of cerebellar function were presented, 2) A clearer picture started to emerge that based on the diversity of what it does, and what we have learned from studies of Ataxia, perhaps we could apply that knowledge to what the cerebellum might be doing in autism, schizophrenia, addiction, and many other neuropsychiatric conditions, and 3) A combined effort from developmental biologists, human geneticists, imagers, electrophysiologists, and behavioral scientists will be required to solve how the cerebellum operates at any given moment, no matter what an individual is doing. This important idea was underscored by the presentation of Dr. Harry Orr, who demonstrated that despite the complexity of motor disease, such as the different Ataxias, perhaps there are common themes in how cells behave, and maybe therapies that target

www.ataxia.org/researchdrive

Les Diablerets Conference Center, Switzerland

Roy Sillitoe, PhD - Baylor College of Medicine

particular cells and at a particular stage of the disease could bring major relief for patients. It was inspiring to see that within the field, such collaborations already exist in the form of inter-institutional and as well international collaborations on research papers and multi-laboratory grants. However, the meeting accomplished the important goals of strengthening existing collaborations and building new ones. The agenda also included a group-wide discussion about how to empower women in science. The session was hosted by Dr. Jennifer Raymond (Stanford) and Dr. Indira Raman (Northwestern). The major accomplishment here was that new statistical data were generated by Dr. Raymond (through a major multi-year effort that has been supported by the journal eLife) and presented to demonstrate the biases in science, and for the first time an open discussion was held about how we might address these problems in our cerebellar research community. Although many more, and regular discussions on the topic must continue in order to fully understand the nature of gender biases, some core issues were defined and all participants were enthusiastic to continue to identify where bias exists in an attempt to eliminate gender inequality. It was strongly felt that discussing issues related to gender in parallel with thinking about ideas to support minorities in science would be a strong approach to improve diversity and creativity in cerebellum research. Based on evaluations we have received from the GRC management, we are delighted to report that that meeting has received lauding reviews, and we thank NAF for playing a critical role in making this important meeting a sensational success.

Attendees of the 2019 Gordon Research Conference - Cerebellum

Jill Sergesketter Napierala, Ph.D.
University of Alabama Birmingham, AL

Research Training Fellowship in Ataxia Cosponsored by the American Academy of Neurology, the American Brain Foundation and the National Ataxia Foundation

Friedreich's ataxia (FRDA) is a severe and progressive neurodegenerative disorder caused by low production of the frataxin protein. Its deficiency leads to complex changes in multiple organs of FRDA patients, with neurons and heart cells being most affected by lower levels of frataxin. As all functions of an organism are interconnected, the deficiency of a single, critical protein has severe consequences for other genes and proteins in cells. Identifying and defining these changes that occur during FRDA requires sensitive analyses of many patient samples. We performed a detailed analysis of all active genes in a large number of FRDA samples and compared the levels of their products to those in unaffected samples. Our data indicated that the levels of a few proteins (enzymes) responsible for eliminating certain cellular toxins are decreased in cells from FRDA patients compared to cells from unaffected individuals. If not kept in balance, the toxins that are usually removed by these enzymes accumulate and cause damage to cell membranes, a process termed lipid peroxidation, which is particularly harmful to neurons and heart cells. The damage caused by these toxins continues to accumulate until the cells are no longer able to repair themselves, which ultimately leads to degeneration of neuronal and cardiac tissues. Importantly, there is evidence linking lipid peroxidation and neuronal cell death in model organisms of FRDA, but no one has investigated role(s) of the toxin-clearing enzymes in FRDA-associated neurodegeneration.

We used engineered neuronal cell line models that we created from FRDA patient fibroblast cells to determine if we could increase the abundance and/or activity of the deficient key enzymes in order to rescue or reverse the damage caused by lipid peroxidation. Our results indicated that in neuronal cells, the levels of only one of the enzymes (aldehyde dehydrogenase 2; ALDH2) was greatly and reproducibly decreased. We treated the FRDA neuronal cells with a drug that is known to increase the activity of ALDH2, called Alda-1, to see if we could reduce the levels of lipid peroxidation in these cells. We first showed that we could increase ALDH2 activity in FRDA neuronal cells following treatment with Alda-1. Then, using two different types of measurements, we showed that treatment of FRDA neuronal cells with Alda-1 resulted in lower overall levels of lipid peroxidation. Our results obtained from neuronal cell models indicate that modulation of ALDH2 activity reduces lipid peroxidation and that it could be considered as a therapeutic target for FRDA. Now, our current studies are focused on testing this idea in FRDA animal models.

BRAIN TISSUE DONATION PROGRAM

Ataxia researchers have made many discoveries because of donations of brain tissue from those affected with Ataxia. NAF's Brain Donation Program was established to allow those who desire to donate their brain upon death so that researchers can find more answers.

If you are interested in learning more about brain donation, you may contact Mary Ann Peterson, NAF Research Assistant, at ***mary_peterson@ataxia.org*** or **763-231-2750**.

Stay up-to-date — Get on our email list

NAF sends emails to keep our members up to date about Ataxia research, events, and other news.

Please email your contact information to ***naf@ataxia.org*** so you don't miss out.

My Story: Living with SCA 6

Tom Likai

My name is Tom, and I am an ataxia sufferer, type six to be specific. I am a 72-year-old veteran, US Army infantry (Vietnam). I spent most of my professional life as a UPS delivery person. I did not experience symptoms until well after I retired. They began as a subtle loss of balance, and they gradually worsened.

About a year ago, I fell while performing one of my balance exercises. Ironically, they were designed to slow the progression of symptoms and "keep me sharp." The fall resulted in a compression fracture of a vertebra in my back, which led to a week in the hospital and three weeks in a rehabilitation facility. These four weeks were more of a challenge and much more unpleasant than my year in a war zone.

The rehabilitation process has long since been completed, and now I simply deal as well as possible with what ataxia has done to me. Living as I do is an interesting combination of opposing factors. In one sense, I am an ideal victim of the tremendous lifestyle alterations a person in my position must endure. I am a homebody if ever there was one – someone who needs very little to be content. I don't like vacations because they disrupt my normal daily routine. I dearly love our house and my wife and being here at home makes me supremely happy.

"Spending time with my wife and just doing things around the house makes my heart feel like singing."

But in another sense, I fit very badly into this curse with which I have been saddled. I am not normally the type to feel deep anger toward other people. But small frustrations with inanimate objects drive me nuts. Yesterday I happened to notice that if I were to consider all the insignificant daily actions I take, I do much less than 50 percent of them right the first time. By "right," I mean as I had intended to do them. My days are filled with attempting to open drawers and grabbing handles wrong, trying to eat a bite of food and missing with the fork, dropping stuff, bumping into stuff, etc. etc.

As a formerly pretty athletic person, this ineptitude is awfully tough to take. To put it mildly, there is very little of a physical nature that I feel equipped to try to do. And as a man, I feel a deep sense of guilt that I am unable to perform basic household functions that I used to do gladly. I miss being a contributing member of this family in a full sense.

In addition to an inability to walk, I can no longer write or talk without scrambling the words. An introverted person like me becomes very quiet around others when he knows in advance that what he wants to say will with near certitude come out wrong. I often have the feeling that just making a statement is like having a fight – like breaking down a door. In the final analysis, it's often not worth the trouble.

To sum up, there is much to my life for which I feel gratitude. I have a richly rewarding hobby (collecting old 45 rpm records) which is multi-faceted, and which keeps me busy for part of every day. I still have the ability to work out at home, which I do for about two and a half hours daily without fail. Keeping fit is extremely meaningful to me. We have a very large yard on a half-acre lot, and I spend almost every spring, fall, and summer day pulling weeds and pruning. And my wife is simply the best individual and the most beautiful person I have ever known. Spending time with her and just doing things around the house makes my heart feel like singing.

But in spite of all this good stuff, I experience mood swings – not as frequently as I used to, but sometimes. The crush of so many frustrations can tend to creep up and take over for five or 10 minutes. Much of it concerns my wife. Although in her sixties, she is young at heart. She wants to do things, many of which are beyond my capacity or outside what has become my comfort area. It hurts to see other people (sisters, friends) fill in for me when what should be husband-wife activities come along. My mantra, I guess one could call it, is to live for each day and to rejoice in what I have rather than to lament what I don't.

Tom is a loving husband, an avid 45 record collector and an Army veteran who enjoys spending time at his home in the Pacific Northwest

Ataxia Tips

for Ataxians... from Ataxians

For many with Ataxia, everyday tasks can become increasingly difficult. One person's shared tip might just be the help someone else needs. See what advice Ataxians are giving to make everyday tasks easier...

Ataxia Tips must be submitted by 11/04/19 to be eligible for inclusion in the next issue of *Generations*. Submit them via email to naf@ataxia.org.

1 Never carry anything if you can figure out a way not to. I keep everything I need to make coffee right next to my coffee maker. I don't use my coffee pot to get water, I use a lidded pitcher. I pour my hot coffee into a lidded commuter cup at the coffee maker and carry that across the room. Speaking of commuter cups, I carry one with me at all times in my purse. I use it anywhere where I'm drinking coffee while not sitting still: church, other's houses, classes, conventions, receptions and etc. (Submitted by Julia Kay Pantoga)

2 I've stopped making pasta that involves pouring hot water into a colander. I make something like penne or rotini, scoop it out of the hot water with a slotted spoon and leave the hot water to cool on the stove before I wash it. (Submitted by Julia Kay Pantoga)

3 When friends visit me, I have them do something small for me, like grate the cheese I'll need for dinner. (Submitted by Julia Kay Pantoga)

4 Everything takes more time and planning. But it is well worth it, because I rarely have spills, burns, or dangerous, messy breakages. (Submitted by Julia Kay Pantoga)

5 Get a stationary or recumbent bike.

a. While holding on to the handlebar with one hand lift the opposite knee towards your chest and vice versa.
b. Hold on to the bar and stand up, lift each knee up to the bar.
c. Sit down, hold on to the bar, stand up, while standing raise up your heels, sit back down.
d. Peddle your bike.
e. Grab the bar, lift yourself to a standing position, stay there and enjoy the fact you are standing, slowly lift your hands off the bar. Your standing on your own if only for a few seconds.
f. Keep trying! (Submitted by Chip Carroll)

Become an Ataxia Advocate

Visit our NEW Advocacy webpage www.ataxia.org/advocacy for advocacy tools, events, and resources.

On the advocacy webpage you can:

- Download the Advocacy Toolkit
- Learn how to contact your representatives and urge them to sign on to support the resolution to have September 25th declared as National Ataxia Awareness Day.
- Check out advocacy events happening around the country.
- Get the latest news on legislative issues impacting the Ataxia community.

We want to hear from you if you have a relationship with a US Congressman or Senator to further support the legislative issues impacting the Ataxia community.

Contact Lori Shogren, Community Program and Services Director at **lori@ataxia.org.**

Have you joined the Ataxia Patient Registry yet?

CoRDS is a centralized international patient registry for all rare diseases; it is based at Sanford Research. The goal of the CoRDS registry is to connect as many patients and researchers as possible to help advance treatments and cures for rare diseases. The CoRDS registry is free for patients to enroll and is available for researchers to access to recruit research participants.

Since 2013, NAF has partnered with CoRDS to enroll participants who have a diagnosis of Ataxia or are at-risk for Ataxia. Since that time, several researchers have accessed the Ataxia registry to help recruit research participants for their important studies. NAF has a goal to have 2,019 people enrolled in the Ataxia registry by 2019. 1,881 participants are currently enrolled.

If you have not enrolled yet, you can register today to help researchers find more answers to Ataxia and to participate in research studies and clinical trials.

CoRDS

SANFORD RESEARCH

Enroll at www.sanfordresearch.org/SpecialPrograms/cords

Questions? Contact CoRDS at cords@sanfordhealth.org or (877)658-9192

JOIN US IN DENVER NEXT YEAR!

63RD ANNUAL ATAXIA CONFERENCE

MARCH 6-7, 2020 • SHERATON DENVER DOWNTOWN HOTEL

PARTNERS IN PROGRESS: THE TIME IS NOW!

Keynote Speaker - Jeremy D. Schmahmann, MD is Professor of Neurology at Harvard Medical School, and a Neurologist at the Massachusetts General Hospital where he is the Founding Director (1994) of the Ataxia Unit, Director of the Laboratory for Neuroanatomy and Cerebellar Neurobiology, and a member of the Cognitive Behavioral Neurology Unit. His research and clinical practice focus on the neurology and basic science of the Ataxias and other cerebellar disorders, and he pioneered the role of the cerebellum in cognition and emotion.

REGISTRATION OPENS NOVEMBER 5, 2019
VISIT **WWW.ATAXIA.ORG** FOR ANNOUNCEMENTS.

SPINOCEREBELLAR ATAXIA TYPE 3 (SCA3)

UNIVERSITY OF MICHIGAN RESEARCH OPPORTUNITY

Do you or a family member suffer from SCA3?

The Neurology Department of the Medical School is currently conducting a research study for the purpose of identifying new biomarkers useful for SCA3, and your help is needed!

We are looking for:

- Healthy individuals and individuals with known SCA3 over 18 yrs. of age
- Approximately 1 hour of your time
- Involves a single lumbar puncture and blood draw
- Paid incentive for participation

Some exclusions apply - contact us at
(734) 232-6247

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

KNOW THE FACTS ABOUT SPINOCEREBELLAR ATAXIA AND A NEW CLINICAL STUDY

About Spinocerebellar Ataxia (SCA)

SCA is an inherited form of ataxia, a rare and progressive neurological disease that develops due to damage to the cerebellum, the part of the brain responsible for coordinating movement.

Ataxia affects nearly 150,000 people living in the U.S. of which an estimated 3,200–18,000 have SCA

Symptoms of SCA may include lack of coordination, trouble with balance, difficulty swallowing, slurred speech and/or deterioration of fine motor skills

The most common types of SCA are SCA1, SCA2, SCA3, SCA6 and SCA7 which are caused by specific genetic defects

People are typically diagnosed in their mid-30s but SCA can affect all ages, genders and race

There is no cure or FDA-approved treatment for SCA

Current treatment approaches focus on symptom management to improve quality of life

SCA Study Overview

The Phase 3 randomized, controlled study is designed to evaluate troriluzole, an investigational drug that modulates the brain chemical glutamate. Brain cells communicate with each another by using chemicals, such as glutamate.

Participants are enrolled in the study for 48 weeks*

** Participants who participate in the study will be eligible to continue for an additional 48 week phase where all participants receive troriluzole.*

Participants are randomized one-to-one on troriluzole or placebo and take two pills once daily

18+ More than 18 U.S. medical centers are participating in the study

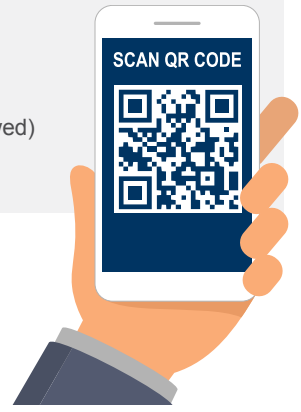
Mainly focus on disease-types SCA1 and SCA2

Study will measure if troriluzole can slow down and improve ataxia symptoms in people with SCA

Primary endpoint = measureable change in ataxia symptoms, including walking, standing, sitting and speech

Key Eligibility Criteria

- Known or suspected diagnosis of SCA1 or SCA2
- Confirmed clinical evidence of SCA diagnosis or willingness to have testing completed
- Ability to walk eight meters without human assistance (canes or other devices are allowed)
- Be physically able to complete the trial (adequate hearing, vision and language skills)



For more information about this study, visit
www.scatrial.org

The study is sponsored by Biohaven Pharmaceuticals.

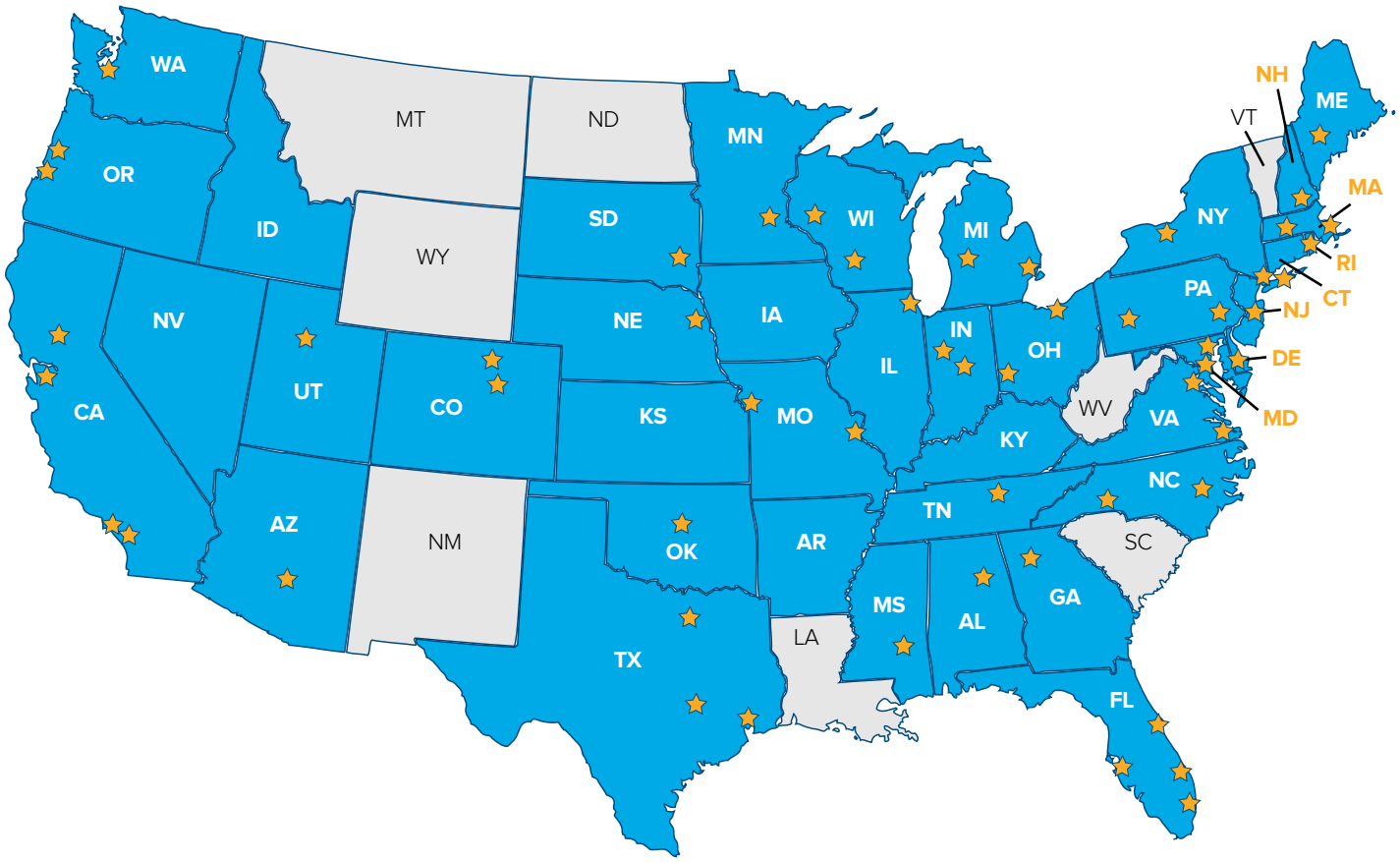
Support Groups & Events

The most current support group and event information is available on the NAF website, www.ataxia.org.

Support groups can remind us that we are not alone. Each person experiences Ataxia in a different way, but we still have many things in common.. A benefit of attending a support group is having the chance to talk with others and learn how different people deal with the same disease.

If you or a loved one has been newly diagnosed with Ataxia, please contact the NAF leader nearest you. If there is not a group in your area, we encourage you to visit our online social networks. You may also consider starting a support group in your area or becoming an NAF ambassador. If you are interested in these volunteer positions please contact Lori Shogren of the NAF staff at lori@ataxia.org or (763) 231-2743.

Come. Learn. Share. But most of all, know that you are NOT alone.



Join one of our Facebook Support Groups!

NAF Support Group	*www.facebook.com/groups/NAFmail*
Under 30 with Ataxia	*www.facebook.com/groups/under30withataxia*
Parents of Ataxia	*www.facebook.com/groups/ParentsOfKidsWithAtaxia*

Support Group News has a new home!

To make your support group news more accessible and timely – we're moving online. To find more support group updates like this, go to ataxia.org/SupportGroupNews at anytime to see the latest news. Want the news delivered to your inbox? We'll send support group news articles in a quarterly email to our members that selected "Support Groups" as an interest when they joined.

Join for free or update your interests at ataxia.org/JoinNAF

Alabama Ataxia Support Group

Submitted by: Becky Donnelly

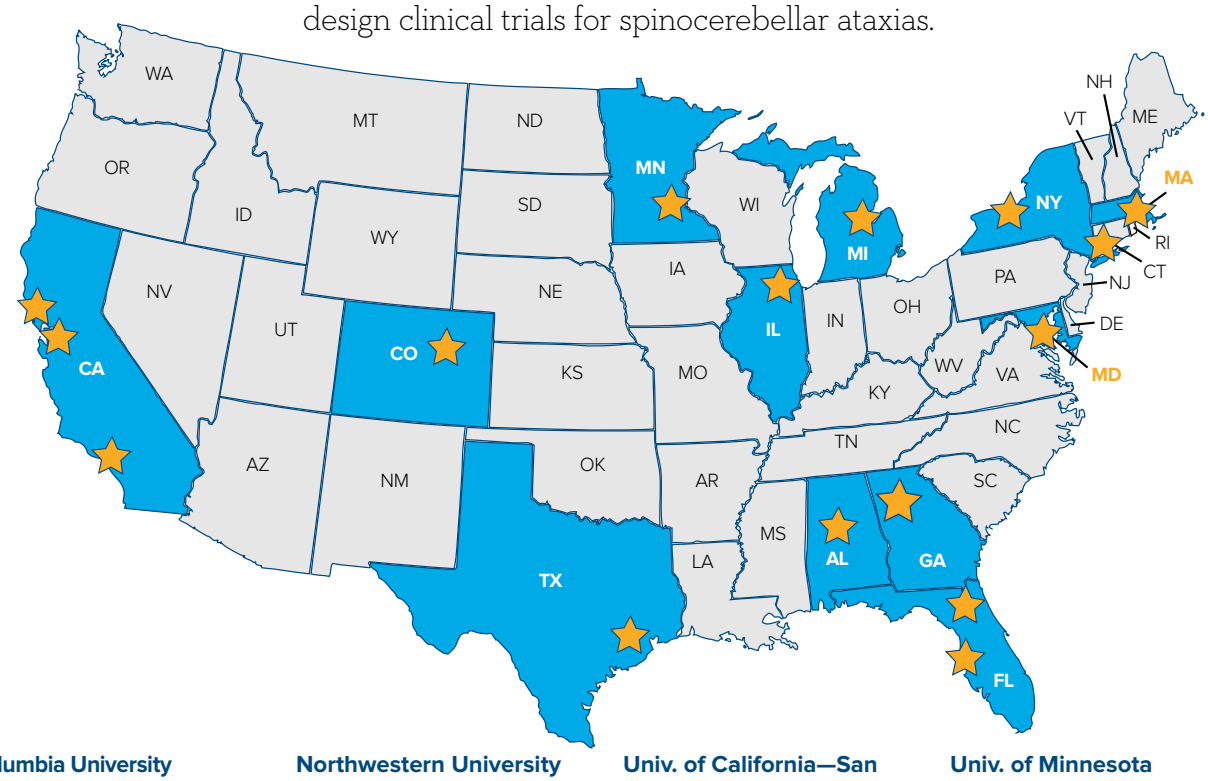
The Alabama Ataxia Support Group met in Double Springs, AL, for their summer social on July 20th, at the Lakeshore Inn and Restaurant. The theme was a Hawaiian Cruise and the dress was colorful island apparel. Elaine and Stephanie greeted members with Aloha as they arrived and planted green grass skirts and leis on them. Pratt provided ukulele music, prompting a happy mood among us. Games with Hawaiian themed movies and songs were enjoyed with prizes for winners. Stephanie taught members to speak Hawaiian (E Komo Mai, Welcome; Mahalo, Thank you; Ono, Delicious; Ohana, Family; A Hui Hou, Until We Meet Again; and E Hele Kaua, Let's Party), and party we did! The party was capped off with the group of 21 members enjoying a delicious meal while overlooking the lake and boats.

Alabama support group members enjoying their Hawaiian Cruise theme dinner

The group is saddened by the death on July 19, 2019, of our long-time member, Jacqueline "Jackie" Rose Guercio. Jackie always had a sweet smile on her face and was beloved by not only our group, but Lakeshore Foundation and many others.

READISCA Observational Study for SCA 1 & 3

This is a major initiative that will provide industry partners with the data they will need in the future to measure whether a treatment or drug is effective to stop or slow down the progressions of the SCAs. The main goals of this study are to establish the world's largest group of early stage and symptomless SCA1 and SCA3 individuals, to validate imaging signs in early stage and symptomless SCA1 and SCA3 individuals and to adapt recent findings to design clinical trials for spinocerebellar ataxias.



Columbia University
New York, NY

Emory University
Atlanta, GA

Houston Methodist Hospital
Houston, TX

Johns Hopkins University
Baltimore, MD

Mass General Hospital (Harvard)
Boston, MA

Northwestern University
Chicago, IL

Stanford University
Palo Alto, CA

Univ. of Alabama—Birmingham
Birmingham, AL

Univ. of California—Los Angeles
Los Angeles, CA

Univ. of California—San Francisco
San Francisco, CA

Univ. of Chicago
Chicago, IL

Univ. of Colorado—Denver
Denver, CO

Univ. of Florida
Gainesville, FL

Univ. of Michigan
Ann Arbor, MI

Univ. of Minnesota
Minneapolis, MN

Univ. of Rochester
Rochester, NY

Univ. of South Florida
Tampa, FL

★ Indicates location of Clinical Trial Site

For more information on READISCA contact:

Houston Methodist Research Institute

Tetsuo Ashizawa, MD—Contact PI/PD

Phone: 346-238-5021 • Email:U01SCA1&3@houstonmethodist.org

Natural History Study needs SCA Research Participants

The Clinical Research Consortium for the Study of Cerebellar Ataxia (CRC-SCA) continues to recruit research participants who have a confirmed diagnosis of SCA 1, 2, 3, 6, 7, 8 or 10. This is an opportunity for anyone in the United States with those forms of SCA at any stage of the disease to participate. Contact the research coordinator at a site near you to learn more about how you might be able to help in Ataxia research efforts to discover a treatment.

The National Ataxia Foundation encourages anyone with SCAs 1, 2, 3, 6, 7, 8 and 10 to participate.

Columbia University
Nadia Amokrane
na2855@cumc.columbia.edu

Emory University
Carole Seeley
carole.seeley@emory.edu

Mass General/Harvard
Jason MacMore
jmacmore@partners.org

Houston Methodist
Titilayo Olubajo
tolubajo@houstonmethodist.org

Johns Hopkins University
Ann Fishman
ann.fishman@jhu.edu

Northwestern University
ZsaZsa Brown
zsazsa.brown@northwestern.edu

University of California Los Angeles
Aaron Fisher
ADFisher@mednet.ucla.edu

University of Florida
Stephen Gullett
Stephen.Gullett@neurology.ufl.edu

University of Chicago
Hannah Casey
hannahcasey@uchicago.edu

University of Michigan
Tasha Kaiser
kaisert@med.umich.edu

University of Minnesota
Diane Hutter
hutte019@umn.edu

University of South Florida
Joshua Vega
joshuavega@health.usf.edu

University of California San Francisco
Julia Glueck
julia.glueck@ucsf.edu

This research is generously supported by the Gordon and Marilyn Macklin Foundation and the National Ataxia Foundation.

Thank you to Dr. Henry Paulson, University of Michigan, who has provided hours of counsel and leadership to make this a successful research endeavor. And, thank you to each of the sites clinical researchers and research coordinators who perform the research necessary to move the field closer to treatments and a cure.

For more information on the study, you may contact Sue Hagen at susan@ataxia.org or 763-231-2742

Disappointed that you don't qualify for this research study?

There is an important step you can take so that in future studies for which you might qualify, you will be notified. And that step is to enroll in the CoRDS Ataxia Patient Registry.

If you are affected with any type of SCA or any other form of ataxia, enroll in the registry by going to the website: https://cordsconnect.sanfordresearch.org/BayaPES/sf/screeningForm?id=SFSFL. If you have questions about enrollment in the registry, contact the CoRDS staff at 877-658-9192.

Memorials and In Your Honor

NAF is grateful to those who have made contributions in memory of or in honor of their friends and families whose names are listed below. This list reflects contributions made in June 2019 - August 2019.

Annie Butler Goldston
Aymee G. Torres, Dr. Aymee A. Torres -Michels, Ricardo Luis Guerrero & Teresita Guerrero
Benjamin Cantor
Berne Hal-Man
Beverly Wright
Bob Williams
Bruce Schneider
Chris and Lisa Crabtree
David D. Brown
David Renz
David W. Henry Jr.
Edna Jackson
Elizabeth "Biffy" Bryson Jordan
Emil Anderson
Frank and Barbara Tinari
Fred & Rick Donnelly
Fred Blum
Gregg Seebohm
Harold Schmidt
Jacqueline Guercio
Janet Bair
Jennifer Hellmans
Jennifer Leader
Joan Fink
Jordan and Sydney Hubbard
Krista Humes
Michael Earkhart
Olivia Schumacher
Paul Aust
Peggy Kapella
Ric Diehl
Robert K. (bob) Tucci (sca6 Research
Robert Morrison Williams
Robert Williams
Rodney Harner
Ron Abarca
Ronald Abarca
Ronald Nardi
Rudy Omictin
Sally Clements
Sharon Baggett
Teresa Kunkle
Tim Green
Tom Fleury
Troy Norton
William Steinlage

NAF Staff Directory and Social Networks

Andrew Rosen, Executive Director	(763) 231-2745 • *andrew@ataxia.org*
Joel Sutherland, Development Director	(763) 231-2748 • *joel@ataxia.org*
Sue Hagen, Patient and Research Services Director	(763) 231-2742 • *susan@ataxia.org*
Lori Shogren, Community Program and Services Director	(763) 231-2743 • *lori@ataxia.org*
Stephanie Lucas, Communications Manager	(763) 231-2744 • *stephanie@ataxia.org*
Mollie Utting, Communications Coordinator	(763) 231-2741 • *mollie@ataxia.org*
Nick Gullickson, Finance Associate	(763) 231-2746 • *nick@ataxia.org*
Jon Wegman, Development Associate	(763) 231-2750 • *jon@ataxia.org*
Mary Ann Peterson, Research Assistant	(763) 231-2747 • *mary.peterson@ataxia.org*
Kelsey Trace, Research Associate	(763) 231-2742 • *kelsey@ataxia.org*

Social Networks:

NAF Facebook Page	*www.facebook.com/ataxiafoundation/*
NAF YouTube Channel	*www.youtube.com/user/NatlAtaxiaFound*
NAF Twitter	*www.twitter.com/NAF_Ataxia*
NAF LinkedIn	*www.linkedin.com/company/nationalataxiafoundation*

BECOME A MEMBER OF NAF TODAY!

Now it's time for action – especially for our current members!

Our new membership enrollment form has new types of membership. Once you enroll with the new form, your membership will not expire. We are working to get everyone converted to the new membership enrollment form. The sooner – the better!

As a member, you will receive:

- News and research opportunities about your specific type of Ataxia as they become avilable
- Early access to free webinars
- eNewsletter and *Generations* publications
- Personalized communication interests

Enroll at www.ataxia.org/JoinNAF

National Ataxia Foundation
600 Hwy 169 s., Ste 1725
Minneapolis, MN 55426
(763) 553-0020

Non-Profit
Organization
U.S. Postage
PAID
Madison, SD
Permit No. 32

2019 RESEARCH DRIVE!
November 1 through December 31...
read more on page 14

Generations is published by the National Ataxia Foundation, Inc., Minneapolis, MN.
Please contact us for permission to reprint or post on the Internet any article from *Generations*.